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I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

09 SEP 2003

Cardiff Road
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1. Your reference GBP290066

2. Patent application number
(The Patent Office will fill in this part) 0321066.3

3. Full name, address and postcode of the or of each applicant (underline all surnames)

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E-28770 Madrid
Spain

857086300.1

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation — Spain

4. Title of the invention New Antitumoral Compounds

5. Name of your agent (if you have one)
"Address for service" in the United Kingdom to which all correspondence should be sent
(including the postcode)

Marks & Clerk
~~57-60 Lincolns Inn fields~~
~~London WC2A 3LS~~

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Patents ADP number (if you know it) 18001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months

Country	Priority application No (if you know it)	Date of filing (day / month / year)

7. Divisionals, etc: Complete this section only if this application is a divisional, application or resulted from an entitlement dispute

Number of earlier application	Date of filing (day / month / year)

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? Yes
(Answer 'Yes' if:
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	0
Description	54
Claim(s)	
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for preliminary examination and search (Patents Form 9/77)	
Request for substantive examination (Patents Form 10/77)	
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

Signature(s) Marks & Clerk Date: 9 September 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

Patent Chemical Formalities
020 7400 3000

#948655

NEW ANTITUMORAL COMPOUNDS

FIELD OF THE INVENTION

The present invention is directed to new kahalalide antitumoral compounds, in particular to analogues of kahalalide F, pharmaceutical compositions containing them and their use as antitumoral, antiviral, antifungal agents and in the treatment of psoriasis.

BACKGROUND OF THE INVENTION

The kahalalide compounds are peptides isolated from a Hawaiian herbivorous marine species of mollusc, *Elysia rufescens* and its diet, the green alga *Bryopsis sp.*. Kahalalide F is described in Hamman *et al.*, J. Am. Chem. Soc., 1993, 115, 5825-5826.

Kahalalide A-G are described in Hamann, M. *et al.*, J. Org. Chem, 1996, 61, 6594-6600: "Kahalalides: bioactive peptides from a marine mollusk *Elysia rufescens* and its algal diet *Bryopsis* sp.".

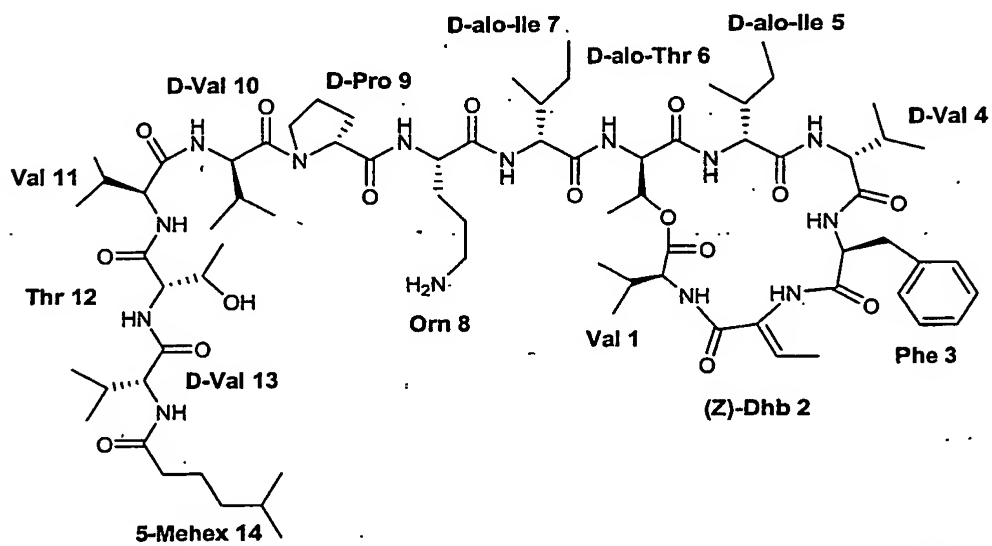
Kahalalide H and J are described in Scheuer P.J. *et al.*, J. Nat. Prod. 1997, 60, 562-567: "Two acyclic kahalalides from the sacoglossan mollusk *Elysia rufescens*".

Kahalalide O is described in Scheuer P.J. et al., J. Nat. Prod. 2000, 63(1) 152-4: "A new depsipeptide from the sacoglossan mollusk Elysia ornata and the green alga Bryopsis species".

For kahalalide K, see Kan, Y. *et al.*, J. Nat. Prod. 1999 62(8) 1169-72: "Kahalalide K: A new cyclic depsipeptide from the hawaiian green alga *bryopsis* species".

For related reports, see also Goetz *et al.*, Tetrahedron, 1999, 55; 7739-7746: "The absolute stereochemistry of Kahalalide F"; Albericio, F. *et al.* Tetrahedron Letters, 2000, 41, 9765-9769: "Kahalalide B. Synthesis of a natural cyclodepsipeptide"; Becerro *et al.* J. Chem. Ecol. 2001, 27(11), 2287-99: "Chemical defenses of the sarcoglossan mollusk *Elysia rufescens* and its host Alga *bryopsis* sp.".

Of the kahalalide compounds, kahalalide F (Formula 1) is the most promising because of its antitumoral activity. Its structure is complex, comprising six amino acids as a cyclic part, and an exocyclic chain of seven amino acids with a terminal fatty acid group.



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Its activity against in vitro cell cultures of human lung carcinoma A-549 and human colon carcinoma HT-29 were reported in EP 610 078. Kahalalide F has also demonstrated to have antiviral and antifungal properties, as well as to be useful in the treatment of psoriasis.

WO 02 36145 describes pharmaceutical compositions containing kahalalide F and new uses of this compound in cancer therapy and is incorporated herein by reference in its entirety.

WO 03 33012 describes the clinical use in oncology of kahalalide compounds and is incorporated herein by reference in its entirety.

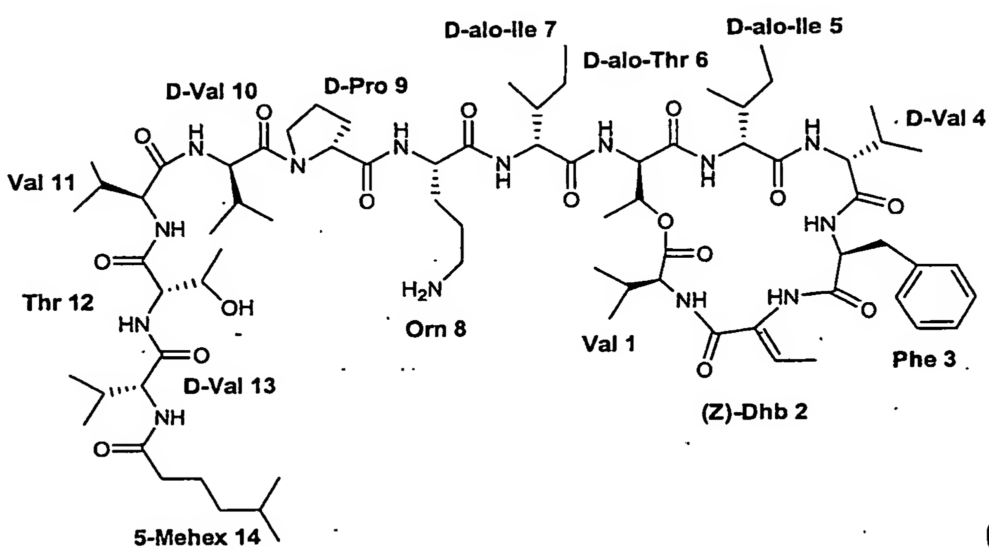
The synthesis and cytotoxic activities of natural and synthetic kahalalide compounds is described in WO 01 58934, which is incorporated herein by reference in its entirety. WO 01 58934 describes the synthesis of Kahalalide F and also of compounds with a similar structure in which the terminal fatty acid chain is replaced by other fatty acids.

There is still a need to provide further antitumoral compounds, in particular further kahalalide compounds with improved properties.

SUMMARY OF THE INVENTION

We have found kahalalide analogue compounds with improved biological activity and an improved process to prepare the kahalalide compounds.

The present invention is directed to compounds of formula 1



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wherein one or more amino acids have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed. The present invention is also directed to compounds of formula 1 wherein the aliphatic acid 5-methylhexanoic acid has been substituted by other carboxylic acids or has been removed.

The present invention is also directed to a pharmaceutical composition comprising a compound as previously defined and a pharmaceutically acceptable carrier, vehicle or diluent.

The present invention further provides a method of treating any mammal, notably a human, affected by cancer or psoriasis which comprises administering to the affected individual a therapeutically effective amount of a compound as defined above.

The present invention can be employed particularly for treatment of patients with refractory cancers that do not respond favourably to other treatments. In particular, the compositions of this invention can be employed after other chemotherapy has been tried and not worked.

The present invention is particularly directed to the treatment of patients affected with prostate cancer, breast cancer, hepatocellular carcinoma, melanoma, colorectal cancer, renal cancer, ovarian cancer, NSCL cancer, epithelial cancer, pancreatic cancer and tumors that overexpress the Her2/neu oncogene.

In another aspect the present invention is directed to the use of a compound as defined above in the manufacture of a medicament. In a preferred embodiment the medicament is for the treatment of cancer, psoriasis, viral infection or fungal infection.

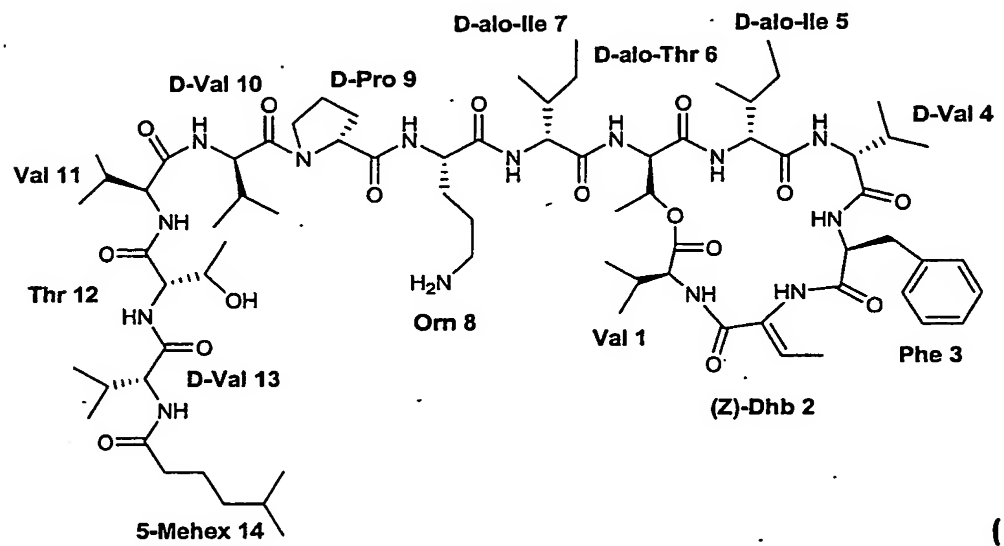
The invention additionally provides kits comprising separate containers containing a pharmaceutical composition comprising a compound as defined above and a reconstituting agent. Methods of reconstitution are also provided.

The invention is also directed to a process for the preparation of a compound as defined above.

DETAILED DESCRIPTION OF THE INVENTION

We have identified analogues of kahalalide F that show significant improvement in activity with respect to kahalalide F.

The present invention is directed to compounds of formula 1



(1)

wherein one or more amino acids have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed. The present invention is also directed to compounds of formula 1 wherein the aliphatic acid 5-methylhexanoic acid has been substituted by other carboxylic acids or has been removed.

Preferred compounds of the invention are those of formula 1 wherein one or more amino acids of the exocyclic chain have been substituted by other natural or non natural amino acids, have been masked with organic groups or have been removed. Examples of such compounds are those of formula 1 wherein there is:

- Glu or Lys instead of Orn in position 8;
- Gly, Phe, Ala, Leu, D-Val, Pro, Gln, Orn, Thr or Glu instead of Val in position 11;
- Val or D-Thr instead of Thr in position 12;
- Gly, D-Ala, D-Leu, D-Phe, D-Pro, Val, D-Glu, D-Gln or D-Thr instead of D-Val in position 13;
- hCh instead of Val in position 11 and/or D-Cha instead of D-Val in position 13; or
- Ala, Gly, Leu, Pro, Glu, Orn or Gln instead of Thr in position 12 and absence of amino acid in position 13.

Besides the modification of the amino acids of the exocyclic chain, there can also be compounds with an additional modification in the fatty acid of the exocyclic chain. Examples of such compounds are those of formula 1 wherein there is:

- Icos, (c/t)-4-Me-cHexa, Und, (4R)-MeHex, (4RS)-MeHex, (4S)-MeHex, Oct, p-MeBza, Bza, p-CF_3Bza, 3,5-dFPhAc, Pipe, p-CF_3Cinn, p-CF_3PhAc, Pfh, 6-OHep, 6,6-dFHep or 4-GuBut instead of 5-MeHex in position 14, and, optionally, Lys instead of Orn in position 8;
- Pro, D-Pip, D-Tic or (5R)-Ph-Pro instead of D-Pro in position 9 and (4S)-MeHex instead of 5-MeHex in position 14;
- $N(Me)_2$,$N'(Me)_2$-Arg, N(Me,Ph),$N'(Me)_2$-Arg, $N(CH_2)_4$,$N'(Me)_2$-Arg, $N(CH_2)_4$,$N'(CH_2)_4$-Arg, $N^{\delta}(CH_2$-$N(CH_2)_4$-$N'(CH_2)_4)$-Orn, $N^{\varepsilon}(Me)_3$-Lys, Orn(N^{δ}Tfa) or Orn(Biot) instead of Orn in position 8, and, optionally (4S)-MeHex instead of 5-MeHex in position 14 and, optionally, Thr(OTfa) instead of Thr in position 12;

- Thr(OTfa) instead of Thr in position 12 and (4S)-MeHex or Lit(OTfa) instead of 5-MeHex in position 14;
- N-$(Hep)_2$-D-Val instead of D-Val in position 13 and there is absence of 5-MeHex in position 14; or
- absence of amino acids in position 11, 12 and 13, and, optionally, Mst instead of 5-MeHex in position 14.

Another preferred compounds of the invention are those of formula 1 wherein one or more amino acids of the cyclic part have been substituted by another natural or non natural amino acid, have been masked with organic groups or have been removed. Examples of such compounds are those of formula 1 wherein there is:

- Dha instead of Thr in position 2;
- D,L-Ser, Gly or Aib instead of Thr in position 2, being the analogues hydrogenated;
- Trp instead of Phe in position 3; or
- D-Thr or D-Ser instead of D-alo-Thr in position 6.

Besides the modification of the amino acids of the cyclic part there can also be compounds with an additional modification in the fatty acid of the exocyclic chain. Examples of such compounds are those of formula 1 wherein there is:

- Phe (3,4-Cl_2), Phe (F_5), Phe (4-I), Phe (4-NO_2), Phe (4-F), Tyr (Me), Thi, Tic, Tyr, Oic, NMePhe, Phe (2-Cl), Phe (3-Cl), Phe (4-Cl), Phe (3,4-F_2), NaI, Bip or Phg instead of hCh in position 3, and, opctionally, (4S)-MeHex or p-CF_3Cinn instead of 5-MeHex in position 14.

Another preferred compounds of the invention are those of formula 1 wherein one or more amino acids of the exocyclic chain and one or more amino acids of the cyclic part have been modified. Examples of such compounds are those of formula 1 wherein there is:

- D-Val or D-Cha instead of D-alo-Ile in positions 5 and 7 and, optionally, D-Cha instead of D-Val in position 4; or
- D-Val instead of Val in position 1, D-Phe instead of Phe in position 3, Val instead of D-Val in position 4, alo-Ile instead of D-alo-Ile in position 5, alo-Thr instead of D-alo-Thr in position 6, alo-Ile instead of D-alo-Ile in position 7, D-Orn instead of Orn in position 8, Pro instead of D-Pro in position 9, Val instead of D-Val in position 10, D-Val instead of Val in position 11, D-Thr instead of Thr in position 12 and Val instead of D-Val in position 13.

The present invention also encompass the pharmaceutically acceptable salts, prodrugs, tautomers, and solvates, thereof.

The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomic forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them.

The compounds of the invention may be in crystalline form either as free compounds or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

The present invention also includes the compounds of the present invention, and the pharmaceutically acceptable salts thereof, wherein one or more hydrogen, carbon or other atoms are replaced by isotopes thereof. Such compounds may be useful as research and diagnostic tools in metabolism pharmacokinetic studies and in binding assays.

As used herein, the compounds of this invention, including the compounds of formula 1, are defined to include pharmaceutically acceptable derivatives or prodrugs thereof. A "pharmaceutically acceptable derivative or prodrug" means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or a metabolite or residue thereof. Particularly favoured derivatives and prodrugs are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an orally administered compound to be more readily absorbed into the blood), enhance delivery of the parent compound to a given biological compartment, increase solubility to allow administration by injection, alter metabolism or alter rate of excretion.

Salts of the compounds of the present invention may comprise acid addition salts derived from a nitrogen in the compound of formula 1 or 2. The therapeutic activity resides in the moiety derived from the compound of the invention as defined herein and the identity of the other component is of less importance although for therapeutic and prophylactic purposes it is, preferably, pharmaceutically acceptable to the patient. Examples of pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulphuric acids, and organic acids, such as tartaric, acetic, trifluoroacetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic and methanesulphonic and arylsulphonic, for example p-toluenesulphonic, acids. A preferred salt is the trifluoro acetic salt.

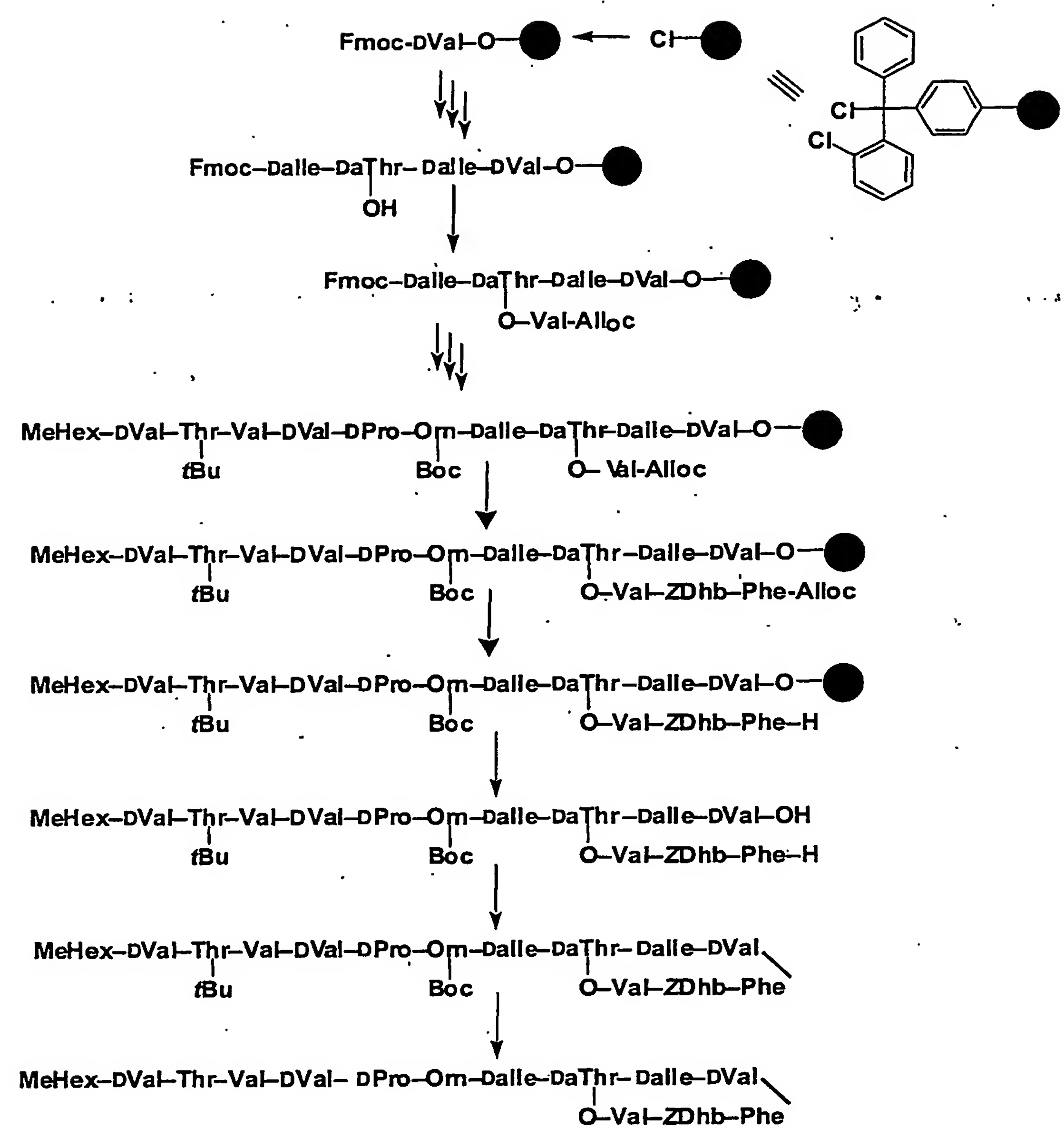
The compounds of the present invention can be prepared according to the synthetic process described in WO 01 58934, or according to the improved process as described herein. Therefore also

encompassed by the invention is a process to prepare a compound according to formula 1.

The key steps of the optimized process for a more economical and safe synthesis of Kahalalide F and its analogues are: (i) partial incorporation of Fmoc-D-Val-OH onto the chlorotritylchloro-polystyrene resin for a initial loading of 0.5 mmol/g; (ii) use as coupling method of DIPCDIC-HOBt, instead of HATU-DIPEA, for the sequential incorporation of the protected amino acids and aliphatic carboxylic acids; (iii) cyclization step with DIPCDI/HOBt/DIPEA in CH_2Cl_2; these conditions avoids two side reaction: epimerisation of the Val residue, which is involved in the activation, and trifluoroacetylation of the Phe or its replacement; (iv) use of sodium diethyl-dithiocarbamate after removing Alloc to avoid presence of Pd (0) in the final product.

The synthesis is preferably a solid phase synthetic process.

The preferred embodiment of the synthetic process of the present invention is best represented in the Scheme 1, which is directed to the formation of the target compounds.



Scheme 1

As shown above in Scheme 1, the preferred process for the synthetic formation of analogues of Kahalalide F is based in a solid-phase approach, see for example Lloyd-Williams, P., *et al. Chemical Approaches to the Synthesis of Peptides and Proteins.* CRC Press, Boca Raton (FL), 1997 and followed with modifications of the method already described for the preparation Kahalalide F and some of its analogues (WO 01 58934).

The process of Scheme 1 comprises the sequential steps of:

(a) incorporating an Fmoc-DVal-OH onto a chlorotrityl chloro resin, forming an ester bond;

(b) elongating the peptidic chain with three amino acids [DaIle, DaThr (free OH), DaIle) using a Fmoc/*t*Bu strategy;

(c) incorporating [Val(1)] using an Alloc/*t*Bu strategy;

(d) elongating the peptidic chain with the remaining amino acids and aliphatic carboxylic acids using a Fmoc/*t*Bu strategy;

(e1) incorporating the dipeptide Alloc-Phe–*Z*Dhb–OH, which has been combined and dehydrated in solution;

(e2a) elongating the peptidic chain with two amino acids, preferably Thr and Phe. The OH of Thr is unprotected and the amino group of Phe, or its replacement, is protected with Fmoc or preferably with Alloc; in some cases if it is protected with Fmoc, this is removed and Alloc is introduced in solid-phase;

(e2b) dehydrating in solid-phase to give the didehydropeptide;

(f) removing the Alloc/Fmoc group of Phe, or of its replacement, while the peptide is still anchored to the solid support;

(g) cleaving the side-chain protected peptide from the solid support;

(h) cyclizing the peptide in solution;

(i) removing TFA labile side chain protecting groups.

(j) Further modifications of functional(s) group(s) in solution phase.

Therefore the process can be conducted as follows:

Fmoc-DVal-OH is incorporated preferably to a chlorotrityl-polystyrene resin, see Barlos, K.; Gatos, D.; Schäfer, W. Angew. Chem. Int. Ed. Engl. 1991, 30, 590-593, in the presence of DIPEA keeping the level of substitution of aprox. 0.5 mmol/g. The use of higher loadings brings the presence of terminated peptides in the final product, see Chiva, C.; Vilaseca, M.; Giralt, E.; Albericio, F. J. Pept. Sci. 1999, 5, 131-140.

Removal of the Fmoc group can be carried out with piperidine–DMF (2:8, v/v) (1 x 2 min, 2 x 10 min). Couplings of Fmoc-aa-OH (4-5 equiv) and the acids at the 14-position can be carried out with DIPCDI-HOBt (equimolar amounts of each one respect to the carboxylic component) or PyBOP-DIPEA (equimolar amount of PyBOP and double amount of DIPEA) in DMF or DMF-Toluene (1:1) for 90 min. After the coupling ninhydrin or chloranil tests are carried out and if it is positive the coupling is repeated in the same conditions, otherwise the process is continued. Washings between deprotection, coupling, and, again, deprotection steps can be carried out with DMF (5 x 0.5 min) and CH_2Cl_2 (5 x 0.5 min) using for example each time 10 mL solvent/g resin.

Incorporation of Alloc-Val-OH (5 equiv) can be carried out with equimolar amount of DIPCDI and 10% of DMAP. This coupling is repeated at least twice.

Removal of Alloc group can be carried out with $Pd(PPh_3)_4$ (0.1

equiv) in the presence of $PhSiH_3$ (10 equiv), see Gómez-Martínez, P.; Thieriet, N.; Albericio, F.; Guibé, F. J. Chem. Soc. Perkin I 1999, 2871-2874, and washing the resin with sodium diethyldithiocarbamate in DMF 0.02 M (3 x 15 min).

The dipeptide Alloc-Phe–ZDhb–OH (4 equiv), which was prepared in solution from Alloc-Phe-OH and H-Thr-O*t*Bu with EDC·HCl, and posterior dehydration and treatment with TFA, can be coupled with DIPCDI–HOAt (4 equiv of each) for 5 h to overnight. The use of other coupling reagents based in HOBt, such as HBTU or DIPCDI–HOBt, has led to incomplete incorporations of the dipeptide.

Dehydration can be carried out in solid-phase with EDC·HCl (water soluble carbodiimide, 20 equiv) in the presence of CuCl (12 equiv) in CH_2Cl_2–DMF (9:1) for 7 days. EDC·HCl/CuCl has been used by dehydration in solution of a residue of Thr in a fragment of Nisin (Fukase, K.; Kitazawa, M.; Sano, A.; Shimbo, K.; Horimoto, S.; Fujita, H.; Kubo, A.; Wakamiya, T.; Shibe, A. Bull. Chem. Soc. Jpn. 1992, 65, 2227-2240) and in solid-phase for the preparation of didehydropeptides from Thr, Ser, and phenylserine (Royo, M.; Jiménez, J.C.; López-Macià, A.; Giralt, E.; Albericio, F. Eur. J. Org. Chem. 2001, 45-48).

Cleavage of the protected peptide from the resin can be accomplished by TFA–CH_2Cl_2 (1:99) (5 x 30 sec).

Cyclization step can be carried out with DIPCDI/HOBt/DIPEA in CH_2Cl_2. These conditions avoid two side reactions: epimerisation of the Val residue, which is involved in the activation, and trifluoroacetylation of the Phe or its replacement.

Final deprotection can be carried out with TFA–H_2O (95:5) for 1 h.

It will be appreciated that the particular choice of protecting groups is not critical, and other choices are widely available. For example, Bzl type groups can replace tBu/Boc; Boc instead of Fmoc; Fmoc instead of Alloc; Wang resin instead of chlorotrityl.

Further detail on the synthesis is given in the examples.

The process of this invention can be carried out from starting materials in an enantio-, stereocontrolled and fast manner, taking advantages of the solid-phase synthetic methodology, where the molecule in construction is bounded to an insoluble support during all synthetic operations.

Pharmaceutical formulations of the compounds of the invention may be adapted for administration by any appropriate route, for example by the oral (including buccal or sublingual), rectal, nasal, topical (including buccal, sublingual or transdermal), vaginal or parenteral (including subcutaneous, intramuscular, intravenous or intradermal) route. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier (s) or excipient (s).

Preferably pharmaceutical compositions of the compounds of the invention include liquid (solutions, suspensions or emulsions) with suitable composition for intravenous administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. Further guidance concerning the pharmaceutical compositions can be found in WO 02 36145 which is incorporated herein by reference in its entirety.

Thus, a combination of a non-ionic surfactant and an organic acid is suited for use with a bulking agent to give a lyophilised form of a compound of the invention suited for reconstitution. Reconstitution is

preferably effected with a mix of emulsifying solubiliser, alkanol and water.

The lyophilised composition preferably comprises mainly the bulking agent, such as at least 90 % or at least 95 % bulking agent. Examples of bulking agents are well known and include sucrose and mannitol. Other bulking agents can be employed.

The non-ionic surfactant in the lyophilised composition is preferably a sorbitan ester, more preferably a polyethylene sorbitan ester, such as a polyoxyethylene sorbitan alkanoate, especially a polyoxyethylene sorbitan mono-oleate, for example polysorbate 80. The non-ionic surfactant typically comprises a few % of the composition, such as 0 to 5 % of the composition, for instance 2 to 3 or 4 % of the composition.

The organic acid in the lyophilised composition is typically an aliphatic acid, preferably a hydroxycarboxylic acid and more preferably a hydroxypolycarboxylic acid, notably citric acid. The organic acid typically comprises a few % of the composition, such as 0 to 5 % of the composition, for instance 2 to 3 or 4 % of the composition.

The amount of the compound of the invention in the lyophilised composition is typically less than 1 %, or often less than 0.1 %, of the mix. A suitable amount is in the range 50 to 200 μg, say about 100 μg, per 100 mg of composition.

The emulsifying solubiliser for the reconstituting agent suitably comprises an polyethylene glycol ester, notably an ester of a fatty acid, more preferably a PEG oleate such as PEG-35 oleate. The emulsifying solubiliser is suitably 0 to 10 % of the reconstituting agent, typically about 3 to 7 %, say about 5 %. The alkanol is usually ethanol, and is suitably 0 to 10 % of the reconstituting agent, typically about 3 to 7 %,

say about 5 %. The remainder of the reconstituting agent is water, and gives a reconstituted solution suited for intravenous injection.

Further dilution of the reconstituted solution with 0.9 % saline may be appropriate for infusion of the kahalalide compound. Suitable infusion equipment preferably includes a glass container, rather than one of polyethylene. Tubing is preferably of silicone.

The preferred reconstituting agent then comprises 2 to 7 %, say about 5 %, emulsifying solubiliser; 2 to 7 %, say about 5 %, alcohol; and remainder water.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use.

The invention additionally provides kits comprising separate containers containing the lyophilised composition and the reconstituting agent. Methods of reconstitution are also provided.

Administration of the compounds or compositions of the present invention is by intravenous infusion. Infusion times of up to 72 hours can be used, more preferably 1 to 24 hours, with either about 1 or about 3 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be around 24 hours or even longer if required.

The administration is performed in cycles, in the preferred application method, an intravenous infusion of a compound of the invention is given to the patients the first week of each cycle, the

patients are allowed to recover for the remainder of the cycle. The preferred duration of each cycle is of either 1, 3 or 4 weeks; multiple cycles can be given as needed. In an alternative dosing protocol, the compound of the invention is administered for say about 1 hour for 5 consecutive days every 3 weeks. Other protocols can be devised as variations.

Dose delays and/or dose reductions and schedule adjustments are performed as needed depending on individual patient tolerance of treatments, in particular dose reductions are recommended for patients with higher than normal serum levels of liver transaminases or alkaline phosphatase.

In one aspect, the present invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a compound of the invention at a dose below 1200 mcg/m2/day, preferably below 930 mcg/m2/day and more preferably below 800 mcg/m2/day. Suitably the dose is at least 320 mcg/m2/day. Preferably the dose is in the range of 400-900 mcg/m2/day, preferably 500-800 mcg/m2/day, more preferably 600-750 mcg/m2/day. Especially preferred are doses of about 650-700 mcg/m2/day.

In a further aspect the invention provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a compound of the invention daily during 5 days at a dose below 930 mcg/m2/day, followed by a resting period of from 1 to 4 weeks in which the kahalalide compound is not administered. The dose is preferably 650-750 mcg/m2/day, more preferably about 700 mcg/m2/day. The infusion time is preferably between 1 and 24 hours, more preferably between 1 and 3 hours. Especially preferred is an infusion time of about 1 or about 3 hours. The resting period is preferably 2-3 weeks, more preferably about 2 weeks.

The present invention also provides a method for treating a human patient afflicted with cancer, comprising administering to said patient a compound of the invention once weekly at a dose below 800 mcg/m2/day. The dose is preferably 600-700 mcg/m2/day, more preferable 650 mcg/m2/day. The infusion time is preferably between 1 and 24 hours, more preferably between 1 and 3 hours.

Although guidance for the dosage is given above, the correct dosage of the compound will vary according to the particular formulation, the mode of application, and the particular situs, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The present invention is particularly directed to the treatment of patients affected with prostate cancer, breast cancer, hepatocellular carcinoma, melanoma, colorectal cancer, renal cancer, ovarian cancer, NSCL cancer, epithelial cancer, pancreatic cancer and tumors that overexpress the Her2/neu oncogene. Most preferably it is directed to the treatment of hepatocellular cancer, melanoma, breast cancer, pancreatic cancer and prostate cancer.

The present invention is also directed to a method of treating a skin disease involving hyperproliferation of dermis cells in a mammal which comprises administering to the mammal an effective, non-toxic amount of a compound of the invention. The skin disease is preferably psoriasis. The present invention is preferably directed to the treatment of human patients affected with psoriasis, in particular severe psoriasis.

The compounds and compositions of this invention may be used

with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, although combination with other chemotherapeutic, hormonal or antibody agents is envisaged. The amounts of the compound of the invention and the other pharmaceutically active agent or agents and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

EXAMPLES

General Procedures. Cl-TrtCl-resin, Protected Fmoc-amino acid derivatives, HOBt, HOAt were from ABI (Framingham, MA), Bachem (Bubendorf, Switzerland), NovaBiochem (Läufelfingen, Switzerland), 4-MeHex derivatives from Narchem, HATU and other guanidylation derivatives were from ABI (Framingham, MA) or prepared as in del Fresno, M.; El-Faham, A.; Carpino, L.A.; Royo, M.; Albericio, F. Organic Lett., 2000, *2*, 3539-3542.

Alloc-amino acids were prepared essentially as described by Dangles et al. see Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet. A. J. Org. Chem. 1987, 52, 4984-4993 and Alloc-*Z*-Dhb-Phe-OH and Kahalalide F as described in WO 01 58934, DIPEA, DIPCDI, EDC·HCl, Piperidine, TFA were from Aldrich (Milwaukee, WI). DMF and CH_2Cl_2 were from SDS (Peypin, France). Acetonitrile (HPLC grade) was from Scharlau (Barcelona, Spain). All comercial reagents and solvents were used as received with exception of CH_2Cl_2, which was passed through a alumina column to remove acidic contaminants.

Solid-phase syntheses were carried out in polypropylene syringes (10-50 mL) fitted with a polyethylene porous disc. Solvents and soluble reagents were removed by suction. Removal of the Fmoc group was

carried out with piperidine–DMF (2:8, v/v) (1 x 2 min, 2 x 10 min). Washings between deprotection, coupling, and, again, deprotection steps were carried out with DMF (5 x 0.5 min) and CH_2Cl_2 (5 x 0.5 min) using each time 10 mL solvent/g resin. Peptide synthesis transformations and washes were performed at 25 °C. Syntheses carried out on solid-phase were controlled by HPLC of the intermediates obtained after cleaving with TFA–H_2O (1:99) for 1 min an aliquot (aprox. 2 mg) of the peptidyl-resin. HPLC reversed phase columns [Nucleosil-C_{18} 4,6 x 250 mm, 10 µm (column A); Nucleosil-C_4 4,6 x 250 mm, 10 µm (column B) were from Sharlau (Spain); Symmetry™ C_{18} 4,6 x 150 mm, 5 µm (column C); Symmetry300™ C_{18} 4,6 x 50 mm, 5 µm (column D) were from Waters (Ireland) and Zorbax SB C_{18} 4,6 x 150 mm, 3.5 µm (column E) was from Agilent (USA)]. Analytical HPLC was carried out on a Waters instrument comprising two solvent delivery pumps (Waters 1525), automatic injector (Waters 717 autosampler), dual wavelength detector (Waters 2487), and system controller (Breeze V3.20) and on a Agilent 1100 instrument comprising two solvent delivery pumps (G1311A), automatic injector (G1329A), DAD (G1315B). UV detection was at 215 or 220 nm, and linear gradients of CH_3CN (+0.036% TFA) into H_2O (+0.045% TFA) were run in the following conditions:

Table I

Chromatographic Conditions	Flow (mL/min)	Gradient (% of CH_3CN)	Running Time (min)
A	1.0	30 to 100	30
B	1.0	40 to 60	15
C	1.0	45 to 60	8
D	1.0	40 to 70	8
E	1.0	45 to 70	8
F	1.0	40 to 70	15
G	1.0	40 to 65	15
H	1.0	10 to 100	30
I	1.0	45 to 65	15

J	1.0	40 to 70	15
K	1.0	55 to 75	15
L	1.0	40 to 100	15
M	1.0	50 to 100	8
N	1.0	35 to 60	15
O	1.0	50 to 100	30
P	1.0	50 to 100	15
Q	1.0	Isocratic at 45	15
R	1.0	30 to 100	15
S	1.0	20 to 100	8
T	0.6	35 to 90	25
U	0.7	40 to 70	50
V	0.8	10 to 48 in 15 min and isocratic 30 min	45
W	1.0	10 to 70	50
X	1.0	10 to 48 in 15 min and isocratic 30 min	45
Y	0.8	10 to 60	50
Z	0.7	15 to 70	55
AB	0.8	10 to 60	55
AC	0.8	30 to 60	45
AD	0.8	10 to 48 in 10 min and isocratic 30 min	40

MALDI-TOF and ES-MS analysis of peptide samples were performed in a PerSeptive Biosystems Voyager DE RP, using DHB matrix, and in a Waters Micromass ZQ spectrometer and in an Agilent Ion Trap 1100 Series LC/MSDTrap. Peptide-resin samples were hydrolyzed in 12 N aqueous HCl-propionic acid (1:1), at 155 °C for 1-3 h and peptide-free samples were hydrolyzed in 6 N aqueous HCl at 155 °C for 1 h. Subsequent amino acid analyses were performed on a Beckman System 6300 autoanalyzer. ^{1}H-NMR spectroscopy [1H, NOESY, TOCSY at (278K)] was performed on a Varian Unity Plus (500 MHz). Chemical shifts (δ) are expressed in parts per million downfield from TMS. Coupling constants are expressed in hertz.

The names of the analogues are referenced to Kahalalide F, indicating between square brackets the modified residue; the suffix "no" indicates the elimination of the natural residue from the sequence.

Example 1

(4S)-MeHex-D-Val-ThrVal-D-Val-D-Pro-Orn-D-*allo*-Ile-cyclo[D-allo-Thr-D-*allo*-Ile-D-Val-Phe-(*Z*)Dhb-Val] [(4S)-MeHex[14]]-Kahalalide F

Step 1

H-D-Val-O-TrtCl-resin.

Cl-TrtCl-resin (1 g, 1.64 mmol/g) was placed in a 20 mL polypropylene syringe fitted with a polyethylene filter disk. The resin was then washed with CH_2Cl_2 (5 x 0.5 min), and a solution of Fmoc-D-Val-OH (238 mg, 0.7 mmol, 0.7 equiv) and DIPEA (0.41 mL) in CH_2Cl_2 (2.5 mL) was added, and the mixture was stirred for 15 min, when extra DIPEA (0.81 mL, total 7 equiv, 7 mmol) and the mixture stirred for 45 min. The reaction was terminated by addition of MeOH (800 µL), after a stirring of 10 min. The Fmoc-D-Val-O-TrtCl-resin was subjected to the following washings/treatments with CH_2Cl_2 (3 x 0.5 min), DMF (3 x 0.5 min), piperidine as indicated in General Procedures, and DMF (5 x 0.5 min). The loading calculated by Fmoc determination was 0.50 mmol/g.

Step 2

Fmoc-D-*allo*-Ile-D-*allo*-Thr(Val-Alloc)-D-*allo*-Ile-D-Val-O-TrtCl-resin.

Fmoc-D-*allo*-Ile-OH (707 mg, 2 mmol, 4 equiv), Fmoc-D-*allo*-Thr-OH (free hydroxy group) (683 mg, 2 mmol, 4 equiv), and Fmoc-D-*allo*-Ile-OH (707 mg, 2 mmol, 4 equiv) were added sequentially to the above obtained H-D-Val-O-TrtCl-resin using DIPCDI (310 µL, 2 mmol, 4 equiv) and HOBt (307 mg, 2 mmol, 4 equiv) in DMF (2.5 mL). In all cases, after

90 min of coupling, the ninhydrin test was negative. Removal of Fmoc group and washings were carried out as described in General Procedures. Alloc-Val-OH (502 mg, 2.5 mmol, 5 equiv) was coupled with DIPCDI (387 mg, 2.5 mmol, 5 equiv) in the presence of DMAP (30.6 mg, 0.25 mmol, 0.5 equiv) and DIPEA (88 µL, 0.5 mmol, 1 equiv) for 45 min. This coupling was repeated in the same conditions twice. An aliqout of the peptidyl-resin was treated with TFA and the HPLC (t_R 7.8 min, conditions S, column D) of the crude obtained after evaporation showed a purity of > 98%. ESMS, calcd for $C_{45}H_{63}N_5O_{11}$, 849.45. Found: *m/z* 850.1 $[M+H]^+$.

Step 3

Fmoc-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-*allo*-Thr(Val-Alloc)-D-*allo*-Ile-D-Val-O-TrtCl-resin.

The Fmoc group was removed and Fmoc-Orn(Boc)-OH (912 mg, 2 mmol, 4 equiv), Fmoc-D-Pro-OH (843 mg, 2.5 mmol, 5 equiv), and Fmoc-D-Val-OH (255 mg, 2.5 mmol, 5 equiv) were sequentially added to the above peptidyl-resin (Example 2) using DIPCDI (310 µL, for 2.0 mmol and 4 equiv; and 388 µL, for 2.5 mmol, 5 equiv) and HOBt (307 mg, for 2.0 mmol and 4 equiv; and 395 mg, 2.5 mmol. 5 equiv) for 90 min. Ninhydrin test after incorporation of Orn and D-Pro was negative. The chloranil after incorporation of D-Val was slightly positive and therefore a recoupling of this residue was carried out with Fmoc-D-Val-OH (678 mg, 2.0 mmol, 4 equiv), DIPCDI (310 µL, 2.0 mmol, 4 equiv) and HOBt (307 mg, 2.0 mmol, 4 equiv) for 90 min. An aliquot of the peptidyl-resin was treated with TFA and the HPLC (t_R 10.1 min, conditions S, column D) of the crude obtained after evaporation showed a purity of > 98 %. MALDI-TOF-MS, calcd for $C_{65}H_{97}N_9O_{16}$, 1,259.71. Found: *m/z* 1,282.16 $[M+Na]^+$.

Step 4

(4*S*)-MeHex-D-Val-Thr(*t*Bu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-*allo*-Thr(Val-Alloc)-D-*allo*-Ile-D-Val-O-TrtCl-resin

The Fmoc group was removed and Fmoc-Val-OH (678 mg, 2 mmol, 4 equiv), Fmoc-Thr(*t*Bu)-OH (992 mg, 2.5 mmol, 5 equiv), Fmoc-D-Val-OH (678 mg, 2 mmol, 4 equiv), and (4*S*)-MeHex-OH (195 mg, 1.5 mmol, 3 equiv) were sequentially added to the above peptidyl-resin (Example 3) using DIPCDI (233 µL, for 1.5 mmol and 3 equiv; 310 µL, for 2 mmol and 4 equiv; and 388 µL, for 2.5 mmol, 5 equiv) and HOBt (230 mg, for 1.5 mmol and 3 equiv; 307 mg, for 2 mmol and 4 equiv; and 395 mg, 2.5 mmol. 5 equiv) for 90 min. In all cases, after 90 min of coupling, the ninhydrin test was negative. Removal of Fmoc group and washings were carried out as described in General Procedures.

Step 5

(4*S*)-MeHex-D-Val-Thr(*t*Bu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-*allo*-Thr(Val-*Z*-Dhb-Phe-Alloc)-D-*allo*-Ile-D-Val-O-TrtCl-resin.

Alloc group was removed with $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 0.1 equiv) in the presence of $PhSiH_3$ (617 µL, 5 mmol, 10 equiv) under atmosphere of Ar and Alloc-Phe-*Z*-Dhb-OH (666 mg, 2 mmol, 4 equiv) and HOAt (273 mg, 2 mmol, 4 equiv) were dissolved in DMF (1.25 mL) and added to peptidyl-resin, then DIPCDI (310 µL, 2 mmol, 4 equiv) was added and the mixture stirred for 5 h, where the ninhydrin test was negative. After washings with DMF and CH_2Cl_2, an aliquot of the peptidyl-resin was treated with TFA–H_2O (1:99) for 1 min and the product was characterized by MALDI-TOF-MS, calcd for $C_{88}H_{146}N_{14}O_{21}$, 1,735.08. Found: *m/z* 1,758.67 $[M+Na]^+$, 1,774.62 $[M+K]^+$.

Step 6

(4*S*)-MeHex-D-Val-Thr(*t*Bu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-*allo*-Thr(Val-*Z*-Dhb-Phe-H)-D-*allo*-Ile-D-Val-OH.

After washings with DMF and CH_2Cl_2, the Alloc group was removed with $Pd(PPh_3)_4$ (58 mg, 0.05 mmol, 0.1 equiv) in the presence of $PhSiH_3$ (617 μL, 5 mmol, 10 equiv) under atmosphere of Ar. The protected peptide was cleaved from the resin by TFA–CH_2Cl_2 (1:99) (5 x 30 sec). Filtrate was collected on H_2O (4 mL) and the H_2O was partially removed in a rotavapor. ACN was then added to dissolve solid that appeared during the H_2O removal, and the solution was lyophilized, to give 639 mg (387 μmol, 77% yield) of the title compound with a purity of > 95 % as checked by HPLC (Condition R, column C, t_R 10.5 min).

Step 7

(4*S*)-MeHex-D-Val-Thr-Val-D-Val-D-Pro-Orn-D-*allo*-Ile-*cyclo*(D-*allo*-Thr-D-*allo*-Ile-D-Val-Phe-*Z*-Dhb-Val)

The protected peptide (Example 6) (639 mg, 387 μmol) was dissolved in CH_2Cl_2 (390 mL, 1 mM), and HOBt (237 mg, 1.55 mmol) dissolved in the minimum volume of DMF to dissolve HOBt, DIPEA (203 μL, 1.16 mmol, 3 equiv), and DIPCDI (240 μL, 1.55 mmol, 4 equiv) were added. The mixture was allowed to stir for 1 h, then the course of the cyclization step was checked by HPLC. The solvent was removed by evaporation under reduced pressure. The protected cyclic peptide was dissolved in TFA–H_2O (19:1, 85 mL) and the mixture was allowed to stir for 1 h. The solvent was removed by evaporation under reduced pressure, and dioxane is added (30 mL) and the solvent is removed by evaporation under reduced pressure (the process was repeated three times), then H_2O (40 mL) was added and lyophilized. The crude product was purified by HPLC (Kromasil C_8 5 μm, 205 x 50 mm), isocratic 44% acetonitrile (+0.05% TFA) in water (+0.05% TFA), 55 mL/h, detection at 220 nm, to give the title product (192 mg, 0.13 mmol, 26% yield, 92.3%). MALDI-TOF-MS, calcd for $C_{75}H_{124}N_{14}O_{16}$, 1,476.93. Found: m/z 1,500.12 $[M+Na]^+$, 1,515.97 $[M+K]^+$. The ^1H-NMR (2.5 mM,

500 MHz, H_2O-D_2O (9:1) spectrum of the compound is indicated in Table II).

Table II

RESIDUE	N-H	Hα	Hβ	OTHER
(Z)-Dhb	9.59 (s)	-	6.63 (q, J =7.5 Hz)	1.19 (d, γ-CH_3)
D-al·lo-Ile 1	8.82 (d, J =9.0 Hz)	4.42	1.8[illegible]	1.25, 1.09, 0.82 (γ-CH_2, γ-CH_3, δ-CH_3)
L-Phe	8.75 (d, J =5.5 Hz)	4.63	3.08 (m)	7.31 (2H Ar, t), 7.25 (3H Ar, d)
D-al·lo-Thr	8.67(d, J =9.0 Hz)	4.64	5.05 (m)	1.21 (γ-CH_3)
D-Val 3	8.13 (d, J =7.5 Hz)	4.33	2.01	0.90 (2 γ-CH_3)
L-Orn	8.29 (d, J =7.5 Hz)	4.31	1.66 (2H)	1.88 (γ-CH_2), 2.96 (bs, δ-CH_2), 7.56 (ε-NH_3^+)
D-al·lo-Ile 2	7.92 (d)	4.18	1.80	1.25, 1.09, 0.81 (γ-CH_2, γ-CH_3, δ-CH_3)
D-Val 5	8.01 (d)	4.08	2.07	0.87 (2 γ-CH_3)
L-Thr	8.19 (d, J =7.5 Hz)	4.29	4.14 (m)	1.13 (γ-CH_3)
D-Val 2	7.89 (d, J =7.5 Hz)	4.32	2.11	0.78 (γ-CH_3)
L-Val 4	8.04 (d)	4.10	2.07	0.90 (2 γ-CH_3)
L-Val 1	7.19 (d, J =9.0 Hz)	4.02	1.52	0.75 (γ-CH_3), 0.65 (d, γ-CH_3)
D-Pro	-	4.36	2.23, 1.99 (m, β-CH_2), 1.85 (m, γ-CH_2), 3.83 (1H, m, δ-CH_2), 3.64 (1H, m, δ-CH_2)	
4(S)-MeHex	-	2.26 (2H)	1.57 (β-CH_2), 1.26, 1.10, 1.33, 0.79 (δ-CH_2, δ-CH_3, γ-CH, ε-CH_3)	

Analogues described in Table III are synthesized following experimental procedures as decribed in Example 1, except the step indicated into the column (Step), where residue(s) (A) have been replaced by other(s) (B) or removed (none).

Table III

Analogue	Example #	Step	Residue Replaced (A)	Residue Incorporated (B)
[D-Thr^6]-KF	2	2	Fmoc-Dallo-Thr-OH 6	Fmoc-D-Thr-OH
		4	(4*S*)-MeHex 14	5-MeHex
[D-Ser^6]-KF	3	2	Fmoc-Dallo-Thr-OH 6	Fmoc-D-Ser-OH
		4	(4*S*)-MeHex 14	5-MeHex
[Glu^8]-KF	4	3	Fmoc-Orn(Boc)-OH 8	Fmoc-Glu(^{t}Bu)-OH
		4	(4*S*)-MeHex 14	5-MeHex
[Lys^8]-KF	5	3	Fmoc-Orn(Boc)-OH 8	Fmoc-Lys(Boc)-OH
		4	(4*S*)-MeHex 14	5-MeHex
[Val^{12}]-KF	6	4	Fmoc-Thr(^{t}Bu)-OH 12	Fmoc-Val-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Thr^{12}]-KF	7	4	Fmoc-Thr(^{t}Bu)-OH 12	Fmoc-D-Thr(^{t}Bu)-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Cha^{13}]-KF	8	4	Fmoc-D-Val-OH 13	Fmoc-D-Cha-OH
			(4*S*)-MeHex 14	5-MeHex
[hCh^{11}]-KF	9	4	Fmoc-Val-OH 11	Fmoc-hCh-OH
			(4*S*)-MeHex 14	5-MeHex
[hCh^{11}, D-Cha^{13}]-KF	10	4	Fmoc-Val-OH 11	Fmoc-hCh-OH
			Fmoc-D-Val-OH 13	Fmoc-D-Cha-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Cha^4, D-Cha^5 ,D-Cha^7]-KF	11	1	Fmoc-D-Val-OH 4	Fmoc-D-Cha-OH
		2	Fmoc-D-alo-Ile-OH 5	Fmoc-D-Cha-OH
		2	Fmoc-D-alo-Ile-OH 7	Fmoc-D-Cha-OH

		4	(4*S*)-MeHex 14	5-MeHex
[D-Val[5], D-Val[7]]-KF	12	2	Fmoc-D-alo-Ile-OH 5	Fmoc-D-Val-OH
		2	Fmoc-D-alo-Ile-OH 7	Fmoc-D-Val-OH
		4	(4*S*)-MeHex 14	5-MeHex
[Icos[14]]-KF	13	4	(4*S*)-MeHex 14	Icosanoic acid
[(c/t)-4-Me-cHexa[14]]-KF	14	4	(4*S*)-MeHex 14	cis/trans-2-(4-Methyl-cyclohexyl)acetic acid
[Und[14]]-KF	15	4	(4*S*)-MeHex 14	Undecanoic acid
[(4*R*)-MeHex[14]]-KF	16	4	(4*S*)-MeHex 14	(4*R*)-Methyl hexanoic acid
[(4*RS*)-MeHex[14]]-KF	17	4	(4*S*)-MeHex 14	(4*RS*)-Methylhexanoic acid
[Oct[14]]-KF	18	4	(4*S*)-MeHex 14	Octanoic acid
[*p*-MeBza[14]]-KF	19	4	(4*S*)-MeHex 14	*p*-Methylbenzoic acid
[Bza[14]]-KF	20	4	(4*S*)-MeHex 14	Benzoic acid
[*p*-CF_3Bza[14]]-KF	21	4	(4*S*)-MeHex 14	*p*-Trifluoromethylbenzoic acid
[3,5-dFPhAc[14]]-KF	22	4	(4*S*)-MeHex 14	3,5-Difluorophenylacetic acid
[Pipe[14]]-KF	23	4	(4*S*)-MeHex 14	Piperonilic acid
[*p*-CF_3Cinn[14]]-KF	24	4	(4*S*)-MeHex 14	*p*-Trifluoromethylcinnamic acid
[*p*-CF_3PhAc[14]]-KF	25	4	(4*S*)-MeHex 14	*p*-Trifluoromethylphenylacetic acid
[Pfh[14]]-KF	26	4	(4*S*)-MeHex 14	Perfluoroheptanoic acid
[6-OHep[14]]-KF	27	4	(4*S*)-MeHex 14	6-Oxoheptanoic acid
[6,6-dFHep[14]]-KF	28	4	(4*S*)-MeHex 14	6,6-Difluoroheptanoic acid
[4-GuBut[14]]-KF	29	4	(4*S*)-MeHex 14	4-([Amino(imino)methyl]amino)butanoic acid
[Lys[8], (4S)-MeHex[14]]-KF	30	3	Fmoc-Orn(Boc)-OH 8	Fmoc-Lys(Boc)-OH
[noVal[11], noThr[12], noD-Val[13]]-KF	31	3	Fmoc-Val-OH 11	none
		4	Fmoc-Thr(tBu)-12	none
		4	Fmoc-D-Val-OH 13	none

		4	(4*S*)-MeHex 14	5-MeHex
[noVal^{11}, noThr^{12}, noD-Val^{13}, Mst^{14}]-KF	32	4	Fmoc-Val-OH 11	none
		4	Fmoc-Thr(tBu)-12	none
		4	Fmoc-D-Val-OH 13	none
		4	(4*S*)-MeHex 14	Myristic (tetradecanoic) acid
[Gly^{13}]-KF	33	4	Fmoc-D-Val-OH 13	Fmoc-Gly-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Ala^{13}]-KF	34	4	Fmoc-D-Val-OH 13	Fmoc-D-Ala-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Leu^{13}]-KF	35	4	Fmoc-D-Val-OH 13	Fmoc-D-Leu-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Phe^{13}]-KF	36	4	Fmoc-D-Val-OH 13	Fmoc-D-Phe-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Pro^{13}]-KF	37	4	Fmoc-D-Val-OH 13	Fmoc-D-Pro-OH
			(4*S*)-MeHex 14	5-MeHex
[Val^{13}]-KF	38	4	Fmoc-D-Val-OH 13	Fmoc-Val-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Glu^{13}]-KF	39	4	Fmoc-D-Val-OH 13	Fmoc-D-Glu-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Gln^{13}]-KF	40	4	Fmoc-D-Val-OH 13	Fmoc-D-Gln-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Thr^{13}]-KF	41	4	Fmoc-D-Val-OH 13	Fmoc-D-Thr-OH
			(4*S*)-MeHex 14	5-MeHex
[Gly^{11}]-KF	42	4	Fmoc-Val-OH 11	Fmoc-Gly-OH
			(4*S*)-MeHex 14	5-MeHex
[Phe^{11}]-KF	43	4	Fmoc-Val-OH 11	Fmoc-Phe-OH
			(4*S*)-MeHex 14	5-MeHex
[Ala^{11}]-KF	44	4	Fmoc-Val-OH 11	Fmoc-Ala-OH
			(4*S*)-MeHex 14	5-MeHex
[Leu^{11}]-KF	45	4	Fmoc-Val-OH 11	Fmoc-Leu-OH
			(4*S*)-MeHex 14	5-MeHex
[D-Val^{11}]-KF	46	4	Fmoc-Val-OH 11	Fmoc-D-Val-OH
			(4*S*)-MeHex 14	5-MeHex
[Pro^{11}]-KF	47	4	Fmoc-Val-OH 11	Fmoc-Pro-OH
			(4*S*)-MeHex 14	5-MeHex
[Gln^{11}]-KF	48	4	Fmoc-Val-OH 11	Fmoc-Gln-OH

			(4*S*)-MeHex 14	5-MeHex
[Orn^{11}]-KF	49	4	Fmoc-Val-OH 11	Fmoc-Orn-OH
			(4*S*)-MeHex 14	5-MeHex
[Thr^{11}]-KF	50	4	Fmoc-Val-OH 11	Fmoc-Thr-OH
			(4*S*)-MeHex 14	5-MeHex
[Glu^{11}]-KF	51	4	Fmoc-Val-OH 11	Fmoc-Glu-OH
			(4*S*)-MeHex 14	5-MeHex
[Ala^{12}, noD-Val^{13}]-KF	52	4	Fmoc-Thr-OH 12	Fmoc-Ala-OH
			Fmoc-D-Val-OH 13	none
[Gly^{12}, noD-Val^{13}]-KF	53	4	(4*S*)-MeHex 14	5-MeHex
			Fmoc-Thr-OH 12	Fmoc-Gly-OH
[Leu^{12}, noD-Val^{13}]-KF	54	4	Fmoc-D-Val-OH 13	none
			(4*S*)-MeHex 14	5-MeHex
[Pro^{12}, noD-Val^{13}]-KF	55	4	Fmoc-Thr-OH 12	Fmoc-Pro-OH
			Fmoc-D-Val-OH 13	none
[Glu^{12}, noD-Val^{13}]-KF	56	4	(4*S*)-MeHex 14	5-MeHex
			Fmoc-Thr-OH 12	Fmoc-Glu-OH
[Orn^{12}, noD-Val^{13}]-KF	57	4	Fmoc-Thr-OH 12	Fmoc-Orn-OH
			Fmoc-D-Val-OH 13	none
[Gln^{12}, noD-Val^{13}]-KF	58	4	Fmoc-L-Thr-OH 12	Fmoc-Gln-OH
			Fmoc-D-Val-OH 13	none
[Pro^{9}, (4S)-MeHex^{14}]-KF	59	4	Fmoc-D-Pro-OH 9	Fmoc-Pro-OH
[D-Pip^{9}, (4S)-MeHex^{14}]-KF	60	4	Fmoc-D-Pro-OH 9	Fmoc-D-Pip-OH
[D-Tic^{9}, (4S)-MeHex^{14}]-KF	61	4	Fmoc-D-Pro-OH 9	Fmoc-D-Tic-OH
[(5R)-Ph-Pro^{9}, (4S)-MeHex^{14}]-KF	62	4	Fmoc-D-Pro-OH 9	Fmoc-(5R)-Ph-Pro-OH

Example 63

5-MeHex-D-Val-Thr(^{t}Bu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-ciclo[D-*allo*-Thr-D-alo-Ile-D-Val-Hch-(*Z*)-Dhb-Val]

Experimental procedures as decribed in Example 1, except that in the step 4 where (4S)-MeHex is replaced by 5-MeHex and in the step 5, which is carried according the following experimental procedure:

Alloc group from 5-MeHex-D-Val-Thr(tBu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-alo-Thr(Val-Alloc)-D-*allo*-Ile-D-Val-O-2-Clorotrityl-Ps (250 mg, initial loading= 0.5 mmol/g resin) was removed as above with $Pd(PPh_3)_4$ in the presence of $PhSiH_3$ under atmosphere of Ar. Fmoc-Thr-OH (free hydroxy group) (213.2 mg; 0.63 mmol; 5 equiv) and Fmoc-hCha-OH (254.0 mg; 0.63 mmol, 5 equiv) were added sequentially to the above peptidyl-resin using DIPCDI (96.8 mg; 0.63 mmol; 5 equiv) and HOBt (85 mg; 0.63 mmol; 5 equiv) in DMF. After extensive washings with DMF (5 x 30 sec), the peptidyl-resin was treated with EDC·HCl (479 mg, 2,5 mmol, 20 equiv), CuCl (184 mg, 1,5 mmol, 12 equiv) in CH_2Cl_2–DMF (1:9) for 6 days. After extensively washings with DMF, CH_2Cl_2, and DMF, experimental protocols as described in example 1 was followed for obtaining the KF analogue.

Analogues described in Table IV are synthesized following experimental procedures as decribed in Example 1, except that in the step 4 where (4S)-MeHex is replaced by 5-MeHex; in the step 5, which is carried as described for example 63, but incorporating Fmoc-Phe-OH instead of Fmoc-hCh-OH, and in the step indicated into the column (Step), where residue(s) (A) have been replaced by other(s) (B) or removed (none).

Table IV

Analogue	Example #	Step	Residue Replaced (A)	Residue Incorporated (B)
[D,L-Ser^2]-KF	64	5[1]	Fmoc-Thr-OH 2	Fmoc-Ser-OH
[Gly^2]-KF	65	5[1]	Fmoc-Thr-OH 2	Fmoc-Gly-OH
[Aib^2]-KF	66	5[1]	Fmoc-Thr-OH 2	Fmoc-Aib-OH
[Dha^2]-KF	67	5	Fmoc-Thr-OH 2	Fmoc-Ser-OH

[1] In analogues 64-66, the reaction of dehydration has not been taken placed, because the analogues are hydrogenated.

[Trp^3]-KF	68	5	Fmoc-Phe-OH 3	Fmoc-Trp-OH
[D-Val^1, D-Phe^3, Val^4, alo-Ile^5, alo-Thr^6, alo-Ile^7, D-Orn^8, Pro^9, Val^{10}, D-Val^{11}, D-Thr^{12}, Val^{13}] KF	69	2	Alloc-Val-OH 1	Alloc-D-Val-OH
		5	Fmoc-Phe-OH 3	Fmoc-D-Phe-OH
		1	Fmoc-D-Val-OH 4	Fmoc-Val-OH
		2	Fmoc-D-*allo*-Ile-OH 5	Fmoc-*allo*-Ile-OH
		2	Fmoc-D-*allo*-Thr-OH 6	Fmoc-*allo*-Thr-OH
		2	Fmoc-D-*allo*-Ile-OH 7	Fmoc-*allo*-Ile-OH
		3	Fmoc-Orn(Boc)-OH 8	Fmoc-D-Orn(Boc)-OH
		3	Fmoc-D-Pro-OH 9	Fmoc-Pro-OH
		3	Fmoc-D-Val-OH 10	Fmoc-Val-OH
		4	Fmoc-Val-OH 11	Fmoc-D-Val-OH
		4	Fmoc-Thr(tBu)-OH 12	Fmoc-D-Thr(tBu-OH
		4	Fmoc-D-Val-OH 13	Fmoc-Val-OH

Analogues described in Table V are synthesized following experimental procedures as decribed in Example 1, except in the step 5, which is carried as described for example 63, and in the step indicated into the column (Step) where residue(s) (A) have been replaced by other(s) (B). Furthermore, before solid-phase dehydratation, the Fmoc group was removed as described in General Procedures, and then the amino group was protected in form of Alloc by reaction with Alloc-OSu (5 equiv) in the presence of DIPEA (5 equiv) using DMF as a solvent (2 hours).

Table V

Analogue	Example #	Step	Residue Replaced (A)	Residue Incorporated (B)
[Phe(3,4-Cl_2)^3, (4S)-$MeHex^{14}$]-KF	70	5	Fmoc-hCh-OH 3	Fmoc-Phe(3,4-Cl_2)-OH
[Phe(F_5)^3, (4S)-$MeHex^{14}$]-KF	71	5	Fmoc-hCh-OH 3	Fmoc-Phe(F_5)-OH
[Phe(4-I)^3, (4S)-$MeHex^{14}$]-KF	72	5	Fmoc-hCh-OH 3	Fmoc-Phe(4-I)-OH

[Phe(4-NO_2)^3, (4S)-MeHex^{14}]-KF	73	5	Fmoc-hCh-OH 3	Fmoc-Phe(4-NO_2)-OH
[Phe(4-F)^3, (4S)-MeHex^{14}]-KF	74	5	Fmoc-hCh-OH 3	Fmoc-Phe(4-F)-OH
[Tyr(Me)^3, (4S)-MeHex^{14}]-KF	75	5	Fmoc-hCh-OH 3	Fmoc-Tyr(Me)-OH
[Thi^3, (4S)-MeHex^{14}]-KF	76	5	Fmoc-hCh-OH 3	Fmoc-Thi-OH
[Tic^3, (4S)-MeHex^{14}]-KF	77	5	Fmoc-hCh-OH 3	Fmoc-Tic-OH
[Tyr^3, (4S)-MeHex^{14}]-KF	78	5	Fmoc-hCh-OH 3	Fmoc-Tyr(tBu)-OH
[Oic^3, (4S)-MeHex^{14}]-KF	79	5	Fmoc-hCh-OH 3	Fmoc-Oic-OH
[*N*MePhe^3, (4S)-MeHex^{14}]-KF	80	5	Fmoc-hCh-OH 3	Fmoc-*N*Me-Phe-OH
[Phe(2-Cl)^3]-KF	81	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Phe(2-Cl)-OH
[Phe(3-Cl)^3]-KF	82	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Phe(3-Cl)-OH
[Phe(4-Cl)^3]-KF	83	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Phe(4-Cl)-OH
[Phe(3,4-F_2)^3]-KF	84	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Phe(3,4-F_2)-OH
[Nal^3]-KF	85	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Nal-OH
[Bip^3]-KF	86	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Bip-OH
[Phg^3]-KF	87	4	(4*S*)-MeHex 14	5-MeHex
		5	Fmoc-hCh-OH 3	Fmoc-Phg-OH
[Phe(3,4-Cl_2)^3, p-CF_3Cinn^{14}]-KF	88	4	(4*S*)-MeHex 14	p-CF_3Cinn-OH
		5	Fmoc-hCh-OH 3	Fmoc-Phe(3,4-Cl_2)-OH

Example 89

[N(Me)$_2$,N'(Me)$_2$-Arg^8]-Kahalalide F

DIPEA (1.73 µL; 10.17 µmol) and HATU (3.86 mg; 10.15 µmol) are added to Kahalalide F (10.0 mg; 6.76 µmol) dissolved in DMF (5 mL). The reaction is followed by HPLC and after 4 h, the DMF is removed under reduced pressure and the residue is disolved in CH_3CN-H_2O-AcOH (4.5:4.5:1, 20 mL), lyophilized, and purified by semipreparative HPLC to give the title analogue (4.5 mg, 40%).

Example 90

[N(Me,Ph),N'(Me)$_2$-Arg^8]-Kahalalide F

Experimental procedures as decribed in example 89, but HAPyU (4.87 mg; 10.15 µmol) is used instead of HATU: 1.63 mg, 12%.

Example 91

[N(CH_2)$_4$,N'(Me)$_2$-Arg^8]-Kahalalide F

Experimental procedures as decribed in example 89, but M_2A (4.12 mg; 10.14 µmol) is used instead of HATU: 5.2 mg, 46%.

Example 92

[N(CH_2)$_4$,N'(CH_2)$_4$-Arg^8]-Kahalalide F (92a) and [N$^\delta$(CH_2-N(CH_2)$_4$-N'(CH_2)$_4$)-Orn^8]-Kahalalide F (92b)

Experimental procedures as decribed in example 89, but BTFFH (containing and impurity of aprox. 50% of 1,1'-(fluoromethylene)dipyrrolidine) (3.16 mg; 10.16 µmol) is used instead of HATU. Two products, 43a and 43b, are obtained and cannot be separated (4.0 mg of the mixture in a proportion 1:1, 35.6%).

HPLC (Cond. A, column A), t_R: 20.8 min (43b) 45% and t_R: 20.9 min (43a) 46%. EM (MALDI-TOF, m/z): (43a) calcd 1,627,05; found 1,630.8 $[M+H]^+$; 1,652.6 $[M+Na]^+$. (43b) calcd 1,629.06; found 1,632.7 $[M+H]^+$; 1,670.6 $[M+K]^+$.

Example 93

[$N^{\varepsilon}(Me)_3$-Lys^8, (4S)-$MeHex^{14}$]-KF

DIPEA (10 µL, 58.8 µmol) and MeI (6µL, 0.100 mmol) are added to [Lys^8, (4S)-$MeHex^{14}$]-Kahalalide F (example 30) (5.0 mg; 3.35 µmol) dissolved in DMF/DCM (1:1, 5 mL). The reaction is followed by HPLC and after 12 h, the solvents are removed under reduced pressure and the residue is disolved in CH_3CN-H_2O-AcOH (4.5:4.5:1, 20 mL), lyophilized, and purified by semipreparative HPLC to give the title analogue (2.2 mg, 44%).

Example 94

[$Thr(OTfa)^{12}$, 4(S)$MeHex^{14}$]-Kahalalide F

[4(S)$MeHex^{14}$]-Kahalalide F (10.0 mg; 6.7 µmol) is disolved in TFA-DCM (1:1, 20 mL) and allowed to stir for 3 days at room temperature. Then, the solvent is removed under reduced pressure and the residue is dissolved in H_2O-CH_3CN (1:9) and purified inmediately minimizing the time in that the sample is dissolved in H_2O. The fractions corresponding to the title analogue in collected in a round bottom flask summerged in liquid N_2 and lyophilized (2.5 mg; 25 %).

Example 95

[$Orn(N^{\delta}Tfa)^8$,$Thr(OTfa)^{12}$, 4(S)$MeHex^{14}$]-Kahalalide F

[(4S)-MeHex[14]]-KF (10 mg; 6.7 μmol) is disolved in DCM (8 mL) and TFAA (18.9 μL; 134 μmol) and DIPEA (22.8 μL; 134 μmol) are added and allowed to react for 12 h. Then, the solvent is removed under reduced pressure, redisolved in H_2O-CH_3CN (1:1), and purified inmediately (2.0 mg, 20 %).

Example 96

[Orn(N^{δ}Tfa)^{8}, 4(S)MeHex^{14}]-Kahalalide F

Experimental procedures as decribed in example 95, but before purification the analogue is dissolved in H_2O-CH_3CN (1:1), left in solution by 2 h, and purified (4,3 mg, 43 %).

Example 97

[Thr(OTfa)^{12}, Lit(OTfa)^{14}]-Kahalalide F

Experimental procedures as decribed in Example 1, except that in the step 4 where (4S)-MeHex is replaced by Lit-OH and in the step 7, the cyclic peptide is dissolved TFA-DCM (1:1, 20 mL) and is allowed to stir for 3 days at room temperature. After this time, the solvent is removed under reduced pressure from an aliquot (10%) and the solid residue is dissolved in H_2O-CH_3CN (1:9) and purified inmediately minimizing the time in that the sample is dissolved in H_2O. The fractions corresponding to the title analogue in collected in a round bottom flask summerged in liquid N_2 and lyophilized (5,6 mg; 6 % yield from starting resin).

Example 98

[no5-MeHex^{14}-*N*-(Hep)$_2$-D-Val^{13}]-Kahalalide F

Experimental procedures as decribed in Example 1, except that in the step 4, heptanaldehyde (60.65 μL; 0.75 mmol; 5 equiv) disolved in DMF-AcOH (99:1; 2 mL) is added to H-D-Val-Thr(tBu)-Val-D-Val-D-Pro-Orn(Boc)-D-*allo*-Ile-D-alo-Thr(Val-Alloc)-D-*allo*-Ile-D-Val-O-2-Clorotrityl-Ps (300 mg; initial loading=0.5 mmol/g resin) and after 5 min, $NaBH_3CN$ (28.28 mg; 0.45 mmol; 3 equiv) disolved in DMF-AcOH (99:1; 1 mL), and the mixture is allowed to react for 2 h, and the treatment is repeated two more times monitoring the reaction by HPLC.

Example 99

[Orn(Biot)⁸]-Kahalalide F

Kahalalide F (150.0 mg; 94.3 μmol), d-Biotine (37.0 mg, 151.5 μmol) and HATU (114.0 mg, 299.8 μmol) are dissolved in DCM anhydrous (6.0 mL) under Ar atmosphere and NMM (58 μL, 524.0 μmol) is added. The mixture is allowed to stir for 20 hours. Then, the solvent is removed under reduced pressure and the residue is dissolved in MeOH and purified. The fractions corresponding to the title analogue are lyophilized (74.0 mg; 43 %).

Characterization of the Kahalalide F analogues

Characterization is showed in Table VI. EM corresponds to MALDI-TOF and the exact mass is calculated by Chemwind 6.0.

Table VI

Analogue	Example #	Chromatography		t_R (min)	Exact mass	Found
		Cond.	Column			
[(4S)-MeHex^{14}]-KF	1	N	C	10.22	1,476.93	1,500.1/1,516.0
[D-Thr^{6}]-KF	2	F	C	7.70	1,476.90	1,477.5/1,499.5/1,515.4

[D-Ser^{6}]-KF	3	F	C	7.30	1,462.92	1,463.4/1,485.4/1,501.4
[Glu^{8}]-KF	4	A	A	19.30	1,491.90	1,514.4/1,530.4
[Lys^{8}]-KF	5	A	A	18.00	1,490.95	1,491.8/1,513.7/1,529.6
[Val^{12}]-KF	6	I	C	12.48	1,474.95	1,496.8/1,513.8
[D-Thr^{12}]-KF	7	B	C	10.21	1,476.93	1,476.6/1,498.6/1,514.5
[D-Cha^{13}]-KF	8	I	C	10.28	1,530.98	1,532.0/1,553.0/1,569.0
[hCh^{11}]-KF	9	J	C	11.79	1,544.99	1,544.6/1,566.3/1,582.3
[hCh^{11}, D-Cha^{13}]-KF	10	K	C	9.77	1,599.04	1,599.2/1,621.3/1,637.3
[D-Cha^{4}, D-Cha^{5} ,D-Cha^{7}]-KF	11	M	E	6.44	1,611.04	1,612.1/1,633.1/1,649.1
[D-Val^{5} ,D-Val^{7}]-KF	12	B	A	8.56	1,448.90	1,448.5/1,470.5/1,486.4
[Icos^{14}]-KF	13	A	B	23.40	1,659.14	1,662.8/1,683.7/1,699.7
[(c/t)-4-Me-cHexa^{14}]-KF	14	A	A	18.80	1,488.93	1,490.9/1,513.9/1,528.9
[Und^{14}]-KF	15	A	A	23.60	1,532.99	1,535.5/1,556.5/1,572.3
[(4R)-MeHex^{14}]-KF	16	J	C	7.29	1,476.93	1,477.8/1,499.8/1,515.7
[(4RS)-MeHex^{14}]-KF	17	J	C	7.29	1,476.93	1,478.5/1,500.5
[Oct^{14}]-KF	18	A	A	12.11	1,490.95	1,491.4/1,512.4/1,528.3
[p-MeBza^{14}]-KF	19	A	A	16.70	1,482.88	1,484.6/1,506.6/1,522.6
[Bza^{14}]-KF	20	A	A	17.10	1,468.87	1,470.5/1,492.5/1,508.5
p-CF$_3$Bza^{14}]-KF	21	A	A	19.90	1,536.86	1,538.1/1,560.0/1,576.0
[3,5-dFPhAc^{14}]-KF	22	A	A	17.30	1,518.87	1,520.6/1,542.6/1,558.6
[Pipe^{14}]-KF	23	A	A	17.20	1,512.86	1,514.2/1,537.2/1,552.1
[p-CF$_3$Cinn^{14}]-KF	24	A	A	14.10	1,562.87	1,564.3/1,586.2/1,602.2
[p-CF$_3$PhAc^{14}]-KF	25	A	A	16.70	1,550.87	1,551.4/1,574.4/1,590.4
[Pfh^{14}]-KF	26	A	A	20.00	1,710.81	1,712.3/1,734.3/1,750.3
[6-OHep^{14}]-KF	27	A	A	13.80	1,490.91	1,492.6/1,514.6/1,531.6
[6,6-dFHep^{14}]-KF	28	A	A	16.44	1,512.91	1,514.5/1,536.4/1,552.4
[4-GuBut^{14}]-KF	29	A	A	12.70	1,491.90	1,493.3/1,516.3/1,532.3
[Lys^{8}, (4S)-MeHex^{14}]-KF	30	Q	C	9.04	1,490.95	1,492.5/1,513.6/1,529.5

[noVal^{11}, noThr^{12}, noD-Val^{13}]-KF	31	A	A	13.70	1,177.75	1,180.9/1,202.9/1,218.8
[noVal^{11}, noThr^{12}, noD-Val^{13}, Mst^{14}]-KF	32	A	A	20.40	1,275.86	1,279.0/1,301.0/1,317.0
[Gly^{13}]-KF	33	T	E	12.70	1,434.89	1,436.5/1,458.0/718.9
[D-Ala^{13}]-KF	34	T	E	13.50	1,448.90	1,450.5/1,472.0/725.7
[D-Leu^{13}]-KF	35	T	E	15.70	1,490.95	1,492.8/1,514.9/746.8
[D-Phe^{13}]-KF	36	T	E	15.70	1,524.93	1,526.5/1,548.9/763.9
[D-Pro^{13}]-KF	37	T	E	14.60	1,474.92	1,476.6/1,498.1/739.0
[Val^{13}]-KF	38	T	E	14.70	1,476.93	1,478.5/1,500.9/739.9
[D-Glu^{13}]-KF	39	T	E	12.90	1,506.91	1,508.8/754.9
[D-Gln^{13}]-KF	40	T	E	12.10	1,505.92	1,506.6/1,528.6
[D-Thr^{13}]-KF	41	AD	E	18.50	1,478.91	1,480.6/1,502.8/741.0
[Gly^{11}]-KF	42	T	E	12.70	1,434.89	1,436.4/1,458.9
[Phe^{11}]-KF	43	W	E	39.70	1,524.93	1,526.6/1,547.6
[Ala^{11}]-KF	44	T	E	13.50	1,448.90	1,449.6/1,471.6
[Leu^{11}]-KF	45	U	E	25.70	1,490.95	1,491.7/1,513.6
[D-Val^{11}]-KF	46	V	E	26.50	1,476.93	1,477.6/1,499.6
[Pro^{11}]-KF	47	X	E	22.20	1,474.92	1,475.6/1,497.6
[Gln^{11}]-KF	48	AC	E	26.50	1,505.92	1,507.0/1,528.9/754.4
[Orn^{11}]-KF	49	Y	E	35.70	1,491.94	1,493.4/1,515.1/747.5
[Thr^{11}]-KF	50	AB	E	46.20	1,478.91	1,480.4/1,501.7/740.9
[Glu^{11}]-KF	51	Z	E	37.30	1,506.91	1,508.5/754.9
[Ala^{12}, noD-Val^{13}]-KF	52	W	E	37.00	1,347.85	1,348.6/1,370.6
[Gly^{12}, noD-Val^{13}]-KF	53	W	E	36.60	1,333.84	1,335.4/1,357.1
[Leu^{12}, noD-Val^{13}]-KF	54	W	E	40.80	1,389.90	1,391.5/1,413.2
[Pro^{12}, noD-Val^{13}]-KF	55	W	E	39.50	1,373.87	1,375.4/1,397.1
[Glu^{12}, noD-Val^{13}]-KF	56	W	E	36.10	1,405.86	1,406.6/1,428.6
[Orn^{12}, noD-Val^{13}]-KF	57	W	E	31.30	1,390.90	1,392.8/1,414.1/697.1
[Gln^{12}, noD-Val^{13}]-KF	58	W	E	35.20	1,404.87	1,406.0/1,428.0

[Pro^{9}, (4S)-MeHex^{14}]-KF	59	R	C	7.68	1,476.83	1,477.3/1,499.3/1,515.2
[D-Pip^{9}, (4S)-MeHex^{14}]-KF	60	R	C	7.45	1,490.95	1,492.2/1,514.2/1,530.2
[D-Tic^{9}, (4S)-MeHex^{14}]-KF	61	R	C	8.17	1,538.95	1,540.1/1,562.1
[(5R)-Ph-Pro^{9}, (4S)-MeHex^{14}]-KF	62	R	C	8.15	1,552.96	1,554.2/1,576.2
[hCh^{3}]-KF	63	G	C	13.20	1,496.99	1,562.0/1,584.0/1,600.0
[D,L-Ser^{2}]-KF	64	B	C	11.15	1,480.93	1,481.1/1,503.1
[Gly^{2}]-KF	65	C	E	4.27	1,450.92	1,450.5/1,472.5/1,488.4
[Aib^{2}]-KF	66	D	E	5.92	1,478.95	1,478.2/1,500.2/1,516.2
[Dha^{2}]-KF	67	E	E	4.43	1,462.92	1,463.3/1,485.3/1,503.2
[Trp^{3}]-KF	68	B	C	10.21	1,515.94	1,516.8/1,538.8/1,554.7
[D-Val^{1}, D-Phe^{3}, Val^{4}, alo-Ile^{5}, alo-Thr^{6}, alo-Ile^{7}, D-Orn^{8}, Pro^{9}, Val^{10}, D-Val^{11}, D-Thr^{12}, Val^{13}]-KF	69	F	C	7.30	1,476.93	1,499.3/1,515.3
[Phe(3,4-Cl$_2$)^{3}, (4S)-MeHex^{14}]-KF	70	R	C	8.52	1,544.85	1,545.7/1,567.6/1,583.6
[Phe(F$_5$)^{3}, (4S)-MeHex^{14}]-KF	71	R	C	8.46	1,566.88	1,567.6/1,589.6/1,605.6
[Phe(4-I)^{3}, (4S)-MeHex^{14}]-KF	72	R	C	8.32	1,602.86	1,603.6/1,625.6/1,641.6
[Phe(4-NO$_2$)^{3}, (4S)-MeHex^{14}]-KF	73	R	C	7.48	1,521.92	1,528.8/1,545.8
[Phe(4-F)^{3}, (4S)-MeHex^{14}]-KF	74	R	C	7.53	1,494.92	1,495.8/1,517.9/1,533.9
[Tyr(Me)^{3}, (4S)-MeHex^{14}]-KF	75	R	C	7.36	1,506.94	1,508.4/1,530.4/1,546.4
[Thi^{3}, (4S)-MeHex^{14}]-KF	76	R	C	7.40	1,482.89	1,482.9/1,504.9/1,520.4
[Tic^{3}, (4S)-MeHex^{14}]-KF	77	R	C	7.85	1,488.93	1,489.4/1,511.4/1,527.4

[Tyr^{3}, (4S)-MeHex^{14}]-KF	78	R	C	6.44	1,492.93	1,493.7/1,515.7/1,531.7
[Oic^{3}, (4S)-MeHex^{14}]-KF	79	R	C	7.99	1,480.96	1,481.4/1,503.4/1,519.4
[*N*MePhe^{3}, (4S)-MeHex^{14}]-KF	80	R	C	8.29	1,490.95	1,491.6/1,513.5
[Phe(2-Cl)^{3}]-KF	81				1,510.89	
[Phe(3-Cl)^{3}]-KF	82				1,510.89	
[Phe(4-Cl)^{3}]-KF	83				1,510.89	
[Phe(3,4-F_2)^{3}]-KF	84				1,512.91	
[Nal^{3}]-KF	85				1,526.95	
[Bip^{3}]-KF	86	R	C	8.70	1,552.96	1554.3/1576.3/1592.3
[Phg^{3}]-KF	87				1,462.92	
[Phe(3,4-Cl_2)^{3}, p-CF_3Cinn^{14}]-KF	88	R	C	9.00	1,630.79	1632.4
[*N*$(Me)_2$,*N′*$(Me)_2$-Arg^{8}]-KF	89	A	A	19.60	1,575.02	1,577.3/1,599.3/1,615.3
[*N*(Me,Ph),*N′*$(Me)_2$-Arg^{8}]-KF	90	A	A	21.10	1,637.03	1,639.4/1,661.3/1,676.3
[*N*$(CH_2)_4$,*N′*$(Me)_2$-Arg^{8}]-KF	91	A	A	21.00	1,601.03	1,602.7/1,623.6/1,640.6
[*N*$(CH_2)_4$,*N′*$(CH_2)_4$-Arg^{8}]-KF	92	A	A	20.80	1,629.06	1,630.8/1,632.7/1,652.6/1,670.6
[N$^{\delta}$(CH-*N*$(CH_2)_4$-*N′*$(CH_2)_4$)-Orn^{8}]-KF				20.90	1,627.05	
[N$^{\varepsilon}$$(Me)_3$-Lys^{8}, (4S)-MeHex^{14}]-KF	93	R	C	7.69	1,534.00	1,534.36
[Thr(OTFA)^{12}, (4S)-MeHex^{14}]-KF	94	L	C	6.18	1,572.91	1,498.7/1,514.7/1,594.6/1,612.5
[Orn(N$^{\delta}$TFA)^{8}, Thr(OTFA)^{12}, (4S)-MeHex^{14}]-KF	95	L	C	13.88	1,668.90	1,670.0/1,677.0/1,693.0/1,574.0/1,596.0

[Orn(NδTFA)8, (4S)-MeHex14]-KF	96	L	C	11.42	1,572.91	1,574.0/1,596.0/1,612.0
[Thr(OTFA)12, Lit(OTFA)14]-KF	97	P	C	14.57	1,915.09	1,916.5/1,938.6/1,820.3/1,842.4/1,724.6/1,746.5/1,762.5
[no5-MeHex14 *N*(Hep)2-Val13, 5-MeHex14]-KF	98	A	A	16.97	1,406.85	1,407.8/1,429.8/1,446.8
[Orn(Biot)8]-Kahalalide F	99	T	E	16.80	1,703.01	1,704.6/1,727.0

Abbreviations used for amino acids and the designations of peptides follow the rules of the IUPAC-IUB Commission of Biochemical Nomenclature in J. Biol. Chem., 1972, 247, 977-983. The following additional abbreviations are used: Alloc, allyloxycarbonyl; $N(CH_2)_4$,$N'(CH_2)_4$-Arg, 2-amino-5-[(dipyrrolidin-1-yl-methylene)-amino]-pentanoic acid; Bip, 2-Amino-3-biphenil-4-yl-propionic acid; Boc, *tert*-butyloxycarbonyl; BTFFH, bis(tetramethylene)fluoroformamidinium hexafluorophosphate; *t*-Bu, *tert*-Butyl; Bza-OH, benzoic acid; Cha, Cyclohexylalanine or 2-amino-3-cyclohexyl-propionic acid; *p*-CF_3Bza-OH, 4-trifluoromethylbenzoic acid; *p*-CF_3BzAc-OH, 3-(4-Trifluoromethylbenzyl)acetic acid; *p*-CF_3Cinn-OH, 3-(4-trifluoromethylbenzyl)acrylic acid; Cl-TrtCl-resin, 2-chlorotrityl chloride-resin; Dha, 2-aminoacrylic acid or didehydroalanine; *Z*-Dhb, *α,β*-didehydro-α-aminobutyric acid; DIPEA, *N,N*-diisopropylethylamine; DMF, *N,N*-dimethylformamide; EDC·HCl, 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride; Fmoc, 9-fluorenylmethoxycarbonyl; 6,6-dFHep-OH, 6,6-difluoro-heptanoic acid; 3,5-dFPhAc-OH, (3,5-difluorophenyl)acetic acid; 4-GuBut-OH, 4-guanidinobutyric acid; GI50, growth inhibition at 50%; HAPyU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; hCh, Homocyclohexylalanine

or 2-amino-4-cyclohexyl-butyric acid; Hep-OH, heptanoic acid; HOAc, acetic acid; HOAt, 1-hydroxy-7-azabenzotriazole (3-hydroxy-3*H*-1,2,3-triazolo-[4,5-*b*]pyridine); HOBt, 1-hydroxybenzotriazole; Icos-OH, icosanoic acid; LC50, Lethal concentration at 50%; Lit-OH, litocholic acid; MeHex-OH, methyhexanoic acid; M_2A, [(tetramethylene)-1*H*-1,2,3-triazolo[4,5-b]pyridino-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate; (c/t-4Me-cHexa)-OH, (cis/trans)-4-methylcyclohexanecarboxylic acid; *p*-MeBza-OH, 4-Methyl-benzoic acid; $N(Me)_2,N'(Me)_2$-Arg, 2-Amino-5-(N',N',N'',N''-tetramethylguanidino)pentanoic acid; $N(CH_2)_4,N'(Me)_2$-Arg, 2-amino-5-[(dimethylamino-pyrrolidin-1-yl-methylene)-amino]-pentanoic acid; MeOH, methanol; $N(Me,Ph),N'(Me)_2$-Arg, 2-amino-5-(N',N',N'-trimethyl-N''-phenyl-guanidino)pentanoic acid; NMM, *N*-methylmorpholine; Mst-OH, Myristic acid or tetradecanoic acid; NaI, 2-Amino-3-naphthalen-2-yl-propionic acid; Oct-OH, Octanoic acid; 6-OHep-OH, 6-Oxo-heptanoic acid; Oic, Octahydro-isoindole-1-carboxylic acid; $[N^{\delta}(CH\text{-}N(CH_2)_4\text{-}N'(CH_2)_4)$-Orn, 2-amino-5-[(dipyrrolidin-1-yl-methyl)-amino]pentanoic acid; Phf-OH, perfluoroheptanoic acid; Phg, Phenyl glycine or Amino-phenyl-acetic acid; (5R)-Ph-Pro, 5-(R)-phenyl-pirrolidine-2-carboxilic acid; Pip, Pipecolic acid; Pipe-OH, benzo[1,3]dioxole-5-carboxilic acid; SPS, solid-phase synthesis; Tfa, trifluoroacetyl; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TGI, total growth inhibition; Thi, Ala-[3-(2-Thienyl)] or 2-amino-3-thiophen-2-yl-propionic acid; Tic, 1,2,3,4-Tetraisoquinoline-3-carboxilic acid; Und-OH, undecanoic acid. Amino acid symbols denote the L-configuration unless stated otherwise. All solvent ratios are volume/volume unless stated otherwise.

Example 100

Biological activity

The bioactivity of compounds of this invention is demonstrated by the results in the following tables obtained in accordance with the methodology described as follows:

The finality of this assay is to interrupt the growth of a "*in vitro*" tumor cell culture by means a continued exhibition of the cells to the sample to be testing.

Cell Lines

NAME	N° ATCC	SPECIES	TISSUE	CHARACTERISTICS
A-549	CCL-185	human	lung	lung carcinoma "NSCL"
SK-MEL-28	HTB-72	human	melanoma	malignant melanoma
HT-29	HTB-38	human	colon	colon adenocarcinoma
LoVo	CCL-229	human	colon	colon adenocarcinoma
LoVo-Dox		human	colon	colon adenocarcinoma (MDR)
DU-145	HTB-81	human	prostate	prostate carcinoma, not androgen receptors
LNCaP	CRL-1740	human	prostate	prostate adenocarcinoma, with androgen receptors
SK-BR-3	HTB-30	human	breast	breast adenocarcinoma, Her2/neu+, (pleural effusion)
IGROV-1		human	ovary	ovary adenocarcinoma
IGROV-ET		human	ovary	ovary adenocarcinoma, characterized as ET-743 resistant cells
SK-OV-3	HTB-77	human	ovary	ovary adenocarcinoma (malignant ascites)
HeLa	CCL-2	human	cervix	cervix epitheloid carcinoma
HeLa-APL	CCL-3	human	cervix	cervix epitheloid carcinoma, characterized as aplidine resistant cells
K-562	CCL-243	human	bone marrow	chronic myelogenous leukemia
PANC-1	CRL-1469	human	pancreas	pancreatic epitheloid carcinoma

HMEC-1		human	endothelium	

A colorimetric type of assay, using sulforhodamine B (SRB) reaction has been adapted for a quantitative measurement of cell growth and viability [following the technique described by Philip Skehan, et al. (1990), New colorimetric cytotoxicity assay for anticancer drug screening, *J. Natl. Cancer Inst.*, 82:1107-1112].

This form of the assay employs 96 well cell culture microplates of 9 mm diameter (Faircloth, 1988; Mosmann, 1983). Most of the cell lines are obtained from American Type Culture Collection (ATCC) derived from different human cancer types.

Cells are maintained in RPMI 1640 10% FBS, supplemented with 0.1 g/l penicillin and 0.1 g/l streptomycin sulfate and then incubated at 37°C, 5% CO_2 and 98% humidity. For the experiments, cells were harvested from subconfluent cultures using trypsin and resuspended in fresh medium before plating.

Cells are seeded in 96 well microtiter plates, at 5×10^3 cells per well in aliquots of 195 μL medium, and they are allowed to attach to the plate surface by growing in drug free medium for 18 hours. Afterward, samples are added in aliquots of 5 μL in a ranging from 10 to 10^{-8} μg/mL, dissolved in DMSO:EtOH:PBS (0.5:0.5:99). After 48 hours exposure, the antitumor effect are measured by the SRB methodology: cells are fixed by adding 50 μL of cold 50% (wt/vol) trichloroacetic acid (TCA) and incubating for 60 minutes at 4°C. Plates are washed with deionized water and dried. One hundred μL of SRB solution (0.4% wt/vol in 1% acetic acid) is added to each microtiter well and incubated for 10 minutes at room temperature. Unbound SRB is removed by washing with 1% acetic acid. Plates are air dried and bound stain is solubilized with Tris buffer. Optical densities are read on a automated spectrophotometric plate reader at a single wavelength of 490 nm.

The values for mean +/- SD of data from triplicate wells are calculated. Some parameters for cellular responses can be calculated: GI = growth inhibition, TGI = total growth inhibition (cytostatic effect) and LC = cell killing (cytotoxic effect).

Tables VII illustrates data on the biological activity of the compounds of the present invention.

Table VII: Activity data (Molar)

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	H[illegible]A-A
1	GI50	3.27E-07	9.00E-07	-	1.58E-07	1.35E-07	4.34E-08	3.15E-07	-	9.07E-07	1.62E-06	1.82E-06	9.54E-08	1.16E-07	6.36E-08	2.54E-07	5.56E-0
	TGI	8,80E-07	2,14E-06	-	3,19E-07	2,89E-07	9,27E-08	4,10E-07	-	2,05E-06	2,96E-06	3,66E-06	2,18E-07	2,42E-07	2,29E-07	7,38E-07	1,52E-0
	LC50	2,54E-06	5,08E-06	-	6,41E-07	6,19E-07	4,69E-07	2,10E-06	-	4,63E-06	5,40E-06	6,77E-06	4,98E-07	5,02E-07	1,43E-06	2,56E-06	3,81E-0
2	GI50	5.29E-06	2.13E-06	-	1.99E-06	1.60E-06	4.47E-06	6.77E-06	-	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	3.06E-06	6.77E-06	6.77E-0
	TGI	6,77E-06	6,77E-06	-	5,33E-06	3,80E-06	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-0
	LC50	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-0
3	GI50	8.33E-07	3.72E-07	-	4.55E-07	2.64E-07	4.06E-07	1.57E-06	-	1.36E-06	5.08E-06	3.08E-06	3.78E-07	1.89E-07	1.79E-07	1.35E-06	1.37E-C
	TGI	1,69E-06	1,12E-06	-	1,27E-06	6,38E-07	6,23E-07	2,66E-06	-	2,46E-06	6,83E-06	6,83E-06	1,22E-06	3,64E-07	3,37E-07	2,64E-06	2,28E-C
	LC50	3,44E-06	2,94E-06	-	3,16E-06	2,11E-06	2,45E-06	4,53E-06	-	4,47E-06	6,83E-06	6,83E-06	3,52E-06	7,58E-07	6,37E-07	5,21E-06	3,78E-C
4	GI50	1.03E-06	3.71E-07	1.95E-07	4.90E-07	8.17E-07	-	2.95E-06	-	1.77E-06	2.11E-06	1.82E-06	8.84E-07	3.48E-07	7.57E-07	-	-
	TGI	2,00E-06	1,19E-06	5,85E-07	1,29E-06	1,69E-06	-	6,70E-06	-	4,02E-06	5,10E-06	3,46E-06	2,00E-06	6,45E-07	1,77E-06	-	-
	LC50	3,88E-06	3,62E-06	2,26E-06	3,31E-06	3,52E-06	-	6,70E-06	-	6,70E-06	6,70E-06	6,60E-06	4,55E-06	2,65E-06	4,15E-06	-	-
5	GI50	1.81E-08	1.42E-08	1.96E-07	1.83E-07	2.40E-07	1.69E-07	8.11E-07	1.56E-08	1.29E-07	7.71E-07	1.14E-06	1.58E-07	1.55E-07	1.62E-07	-	-
	TGI	3,20E-08	2,61E-08	4,08E-07	3,71E-07	4,88E-07	3,06E-07	1,87E-06	2,63E-08	2,75E-07	1,65E-06	2,37E-06	2,81E-07	2,71E-07	2,98E-07	-	-
	LC50	5,69E-08	4,79E-08	1,49E-06	1,23E-06	2,83E-06	5,54E-07	4,30E-06	4,46E-08	5,82E-07	3,55E-06	4,92E-06	4,98E-07	4,78E-07	5,52E-07	-	-
6	GI50	1.65E-07	3.13E-07	-	1.50E-07	1.54E-07	1.02E-07	1.75E-07	-	2.57E-07	6.61E-07	1.02E-06	1.48E-07	1.33E-07	1.59E-07	1.44E-07	3.79E-(
	TGI	2,94E-07	1,00E-06	-	2,99E-07	2,91E-07	2,22E-07	2,94E-07	-	8,54E-07	1,44E-06	1,96E-06	2,68E-07	2,48E-07	2,83E-07	2,63E-07	1,04E-(
	LC50	5,23E-07	2,78E-06	-	5,98E-07	5,49E-07	4,82E-07	4,92E-07	-	2,36E-06	3,07E-06	3,80E-06	4,85E-07	4,63E-07	5,03E-07	4,80E-07	3,11E-(
7	GI50	6.77E-06	6.04E-06	-	6.77E-06	6.77E-06	6.77E-06	6.77E-06	-	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	5.14E-06	6.77E-06	6.77E-(
	TGI	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-(
	LC50	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	-	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-(
8	GI50	1.33E-06	2.79E-06	-	1.04E-06	6.52E-07	4.84E-07	1.45E-06	-	1.97E-06	1.93E-06	6.53E-06	9.92E-07	1.01E-06	9.86E-07	1.40E-06	1.70E-(
	TGI	2,38E-06	6,53E-06	-	2,11E-06	1,44E-06	1,25E-06	2,42E-06	-	4,18E-06	4,92E-06	6,53E-06	1,99E-06	1,96E-06	2,09E-06	2,30E-06	2,87E-(
	LC50	4,26E-06	6,53E-06	-	4,29E-06	3,16E-06	3,17E-06	4,02E-06	-	6,53E-06	6,53E-06	6,53E-06	3,99E-06	3,82E-06	4,43E-06	3,80E-06	4,86E-(
9	GI50	4.55E-07	9.25E-07	-	2.37E-07	2.78E-07	1.49E-07	3.21E-07	-	1.84E-07	1.72E-06	2.25E-06	8.60E-08	9.57E-08	5.07E-08	3.56E-07	3.91E-(
	TGI	1,24E-06	2,33E-06	-	7,76E-07	8,09E-07	3,66E-07	9,44E-07	-	4,48E-07	3,39E-06	5,27E-06	1,92E-07	1,93E-07	1,30E-07	1,12E-06	1,20E-(
	LC50	3,28E-06	5,85E-06	-	3,31E-06	2,94E-06	1,36E-06	2,62E-06	-	1,64E-06	6,47E-06	6,47E-06	4,29E-07	3,90E-07	3,05E-07	2,92E-06	2,75E-(
10	GI50	4.29E-06	4.89E-06	-	1.99E-06	2.23E-06	1.31E-06	3.10E-06	-	3.56E-06	6.25E-06	-	1.06E-06	1.12E-06	5.37E-07	2.67E-06	3.67E-(
	TGI	6,25E-06	6,25E-06	-	3,84E-06	4,56E-06	2,32E-06	6,25E-06	-	6,25E-06	6,25E-06	-	1,96E-06	2,27E-06	1,30E-06	6,25E-06	6,25E-(
	LC50	6,25E-06	6,25E-06	-	6,25E-06	6,25E-06	4,16E-06	6,25E-06	-	6,25E-06	6,25E-06	-	3,58E-06	4,59E-06	2,94E-06	6,25E-06	6,25E-(
11	GI50	2.20E-07	6.45E-07	-	1.90E-07	1.33E-07	1.06E-07	4.55E-07	-	1.32E-07	1.58E-06	1.43E-06	9.74E-08	9.74E-08	8.19E-08	2.23E-07	2.11E-(
	TGI	8,56E-07	1,40E-06	-	5,67E-07	3,03E-07	2,52E-07	1,28E-06	-	2,60E-07	2,56E-06	2,74E-06	1,91E-07	1,99E-07	1,64E-07	8,93E-07	8,31E-(
	LC50	2,64E-06	3,01E-06	-	2,99E-06	1,29E-06	5,99E-07	3,03E-06	-	5,11E-07	4,14E-06	5,25E-06	3,77E-07	4,06E-07	3,26E-07	2,55E-06	2,32E-(
12	GI50	1.61E-06	2.80E-06	-	1.85E-06	1.79E-06	1.74E-06	1.68E-06	-	2.17E-06	3.19E-06	4.67E-06	1.29E-06	1.26E-06	9.52E-07	1.75E-06	3.02E-(
	TGI	2,82E-06	3,79E-06	-	3,01E-06	2,97E-06	3,06E-06	3,12E-06	-	6,68E-06	5,46E-06	6,90E-06	2,51E-06	2,28E-06	1,97E-06	2,98E-06	6,01E-(
	LC50	4,92E-06	5,14E-06	-	4,93E-06	4,93E-06	5,38E-06	5,78E-06	-	6,90E-06	6,90E-06	6,90E-06	4,88E-06	4,13E-06	4,08E-06	5,07E-06	6,90E-
13	GI50	1.28E-06	1.21E-06	-	1.36E-06	1.66E-06	8.61E-07	1.25E-06	-	1.18E-06	1.23E-06	2.02E-06	1.26E-06	9.03E-07	-	1.40E-06	1.25E-
	TGI	2,28E-06	2,39E-06	-	2,52E-06	2,81E-06	1,86E-06	2,21E-06	-	2,13E-06	2,42E-06	5,48E-06	2,32E-06	1,79E-06	-	2,71E-06	2,23E-
	LC50	4,04E-06	4,73E-06	-	4,68E-06	4,79E-06	3,99E-06	3,93E-06	-	3,82E-06	4,71E-06	6,02E-06	4,28E-06	3,58E-06	-	5,25E-06	3,98E-
14	GI50	6.12E-07	1.34E-06	-	3.82E-07	8.46E-07	1.52E-07	8.86E-07	-	9.33E-07	2.02E-06	2.01E-06	1.89E-07	9.93E-08	1.44E-07	7.79E-07	6.11E-
	TGI	1,48E-06	2,87E-06	-	1,22E-06	1,94E-06	3,17E-07	1,89E-06	-	2,15E-06	3,58E-06	6,71E-06	4,22E-07	2,34E-07	2,88E-07	1,84E-06	1,72E-
	LC50	3,36E-06	6,11E-06	-	3,47E-06	4,47E-06	6,57E-07	4,01E-06	-	4,95E-06	6,32E-06	6,71E-06	1,83E-06	5,50E-07	5,76E-07	4,37E-0[illegible]	4,56E-

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	H[illegible]A-A
15	GI50	1.62E-07	5.29E-07	-	1.58E-07	2.35E-07	2.67E-08	1.69E-07	1.43E-07	1.15E-06	1.23E-06	1.27E-07	1.17E-07	4.08E-08	1.20E-07	2.29E-0
	TGI	3,53E-07	1,44E-06	-	3,72E-07	8,41E-07	7,43E-08	4,45E-07	3,39E-07	2,18E-06	2,28E-06	2,70E-07	2,67E-07	1,65E-07	2,65E-07	8,47E-0
	LC50	1,04E-06	3,48E-06	-	1,54E-06	3,34E-06	4,68E-07	2,04E-06	1,69E-06	4,10E-06	4,20E-06	5,74E-07	6,04E-07	4,78E-07	5,88E-07	3,55E-0
16	GI50	1.20E-06	1.50E-06	-	9.41E-07	8.05E-07	1.25E-06	1.14E-06	1.20E-06	3.73E-06	4.70E-06	7.38E-07	2.48E-07	2.88E-07	1.05E-06	1.56E-0
	TGI	2,14E-06	2,46E-06	-	1,81E-06	1,62E-06	2,20E-06	2,09E-06	2,26E-06	6,77E-06	4,24E-06	1,54E-06	7,78E-07	7,71E-07	1,93E-06	3,47E-0
	LC50	3,82E-06	4,04E-06	-	3,50E-06	3,26E-06	3,86E-06	3,80E-06	4,24E-06	6,77E-06	4,24E-06	3,22E-06	2,28E-06	2,19E-06	3,55E-06	6,77E-0
17	GI50	2.52E-07	9.34E-07	-	1.85E-07	2.09E-07	1.62E-07	1.30E-06	2.40E-07	2.37E-06	3.82E-06	1.47E-07	1.41E-07	1.80E-07	7.44E-07	7.58E-0
	TGI	8,39E-07	2,10E-06	-	3,96E-07	4,24E-07	3,14E-07	2,54E-06	7,51E-07	4,07E-06	6,77E-06	2,84E-07	2,67E-07	3,66E-07	1,71E-06	1,86E-0
	LC50	2,65E-06	4,75E-06	-	1,49E-06	1,84E-06	6,06E-07	4,96E-06	2,89E-06	6,77E-06	6,77E-06	5,50E-07	5,03E-07	1,27E-06	3,92E-06	4,59E-0
18	GI50	1.49E-07	4.02E-07	-	1.68E-07	1.47E-07	1.21E-07	6.70E-07	1.34E-07	2.41E-06	2.01E-06	2.01E-07	1.88E-07	1.07E-07	2.88E-07	5.36E-0
	TGI	6,70E-07	1,34E-06	-	3,02E-07	3,02E-07	3,02E-07	1,14E-06	2,82E-07	3,02E-06	3,35E-06	3,22E-07	2,68E-07	1,68E-07	8,04E-07	1,07E-0
	LC50	1,47E-06	3,35E-06	-	1,07E-06	2,01E-06	5,36E-07	1,68E-06	1,21E-06	4,02E-06	6,03E-06	5,36E-07	4,02E-07	3,35E-07	1,68E-06	3,35E-0
19	GI50	7.75E-07	1.02E-06	-	3.43E-07	4.39E-07	1.70E-07	1.16E-06	7.75E-07	7.62E-07	2.06E-06	3.14E-07	1.20E-07	-	8.49E-07	9.23E-0
	TGI	1,73E-06	2,55E-06	-	1,37E-06	1,44E-06	3,77E-07	2,24E-06	1,71E-06	2,01E-06	6,74E-06	1,12E-06	2,35E-07	-	1,95E-06	2,00E-0
	LC50	3,87E-06	6,42E-06	-	4,23E-06	4,07E-06	1,40E-06	4,31E-06	3,76E-06	5,30E-06	6,74E-06	3,42E-06	4,58E-07	-	4,48E-06	4,36E-0
20	GI50	9.39E-07	1.18E-06	-	7.14E-07	7.55E-07	3.20E-07	1.20E-06	9.52E-07	3.05E-07	3.79E-06	6.94E-07	1.28E-07	-	1.11E-06	1.01E-0
	TGI	1,99E-06	2,87E-06	-	1,73E-06	1,78E-06	1,16E-06	2,26E-06	1,95E-06	2,12E-06	6,80E-06	1,64E-06	3,03E-07	-	2,30E-06	2,08E-0
	LC50	4,25E-06	6,80E-06	-	4,20E-06	4,20E-06	3,38E-06	4,23E-06	3,97E-06	6,80E-06	6,80E-06	3,88E-06	8,10E-07	-	4,76E-06	4,27E-0
21	GI50	2.41E-07	3.39E-07	-	1.77E-07	1.69E-07	1.11E-07	8.97E-07	1.46E-07	6.50E-06	1.30E-06	1.14E-07	9.17E-08	-	3.19E-07	5.04E-0
	TGI	1,22E-06	1,30E-06	-	7,22E-07	7,61E-07	2,46E-07	1,85E-06	4,06E-07	6,50E-06	3,11E-06	2,59E-07	1,92E-07	-	1,28E-06	1,48E-0
	LC50	3,28E-06	3,52E-06	-	3,45E-06	2,83E-06	5,43E-07	3,80E-06	1,68E-06	6,50E-06	6,50E-06	5,85E-07	4,04E-07	-	3,91E-06	3,67E-0
22	GI50	1.43E-06	1.64E-06	-	9.80E-07	1.07E-06	4.64E-07	2.50E-06	1.17E-06	6.58E-06	5.45E-06	8.88E-07	2.88E-07	-	1.29E-06	1.96E-0
	TGI	6,58E-06	6,58E-06	-	2,12E-06	2,32E-06	1,45E-06	6,58E-06	2,16E-06	6,58E-06	6,58E-06	1,94E-06	1,06E-06	-	3,28E-06	6,58E-0
	LC50	6,58E-06	6,58E-06	-	4,57E-06	5,01E-06	3,64E-06	6,58E-06	3,99E-06	6,58E-06	6,58E-06	4,25E-06	3,11E-06	-	6,58E-06	6,58E-0
23	GI50	-	-	-	-	-	-	-	6.61E-07	-	-	1.32E-07	-	-	-	-
	TGI	-	-	-	-	-	-	-	1,98E-06	-	-	3,30E-07	-	-	-	-
	LC50	-	-	-	-	-	-	-	4,62E-06	-	-	5,28E-07	-	-	-	-
24	GI50	4.77E-08	9.78E-08	5.95E-08	9.98E-08	3.32E-08	-	1.89E-07	1.20E-07	8.82E-07	1.32E-06	1.38E-07	1.12E-07	5.73E-08	-	-
	TGI	1,30E-07	2,65E-07	1,52E-07	2,39E-07	6,29E-08	-	3,98E-07	3,73E-07	1,84E-06	2,34E-06	2,54E-07	2,25E-07	1,81E-07	-	-
	LC50	3,41E-07	1,25E-06	3,70E-07	5,70E-07	2,92E-07	-	1,63E-06	4,02E-06	3,80E-06	4,16E-06	4,69E-07	4,54E-07	5,67E-07	-	-
25	GI50	2.51E-07	3.20E-07	1.26E-07	2.52E-07	2.00E-07	-	1.40E-06	2.97E-07	1.42E-06	1.58E-06	5.55E-07	2.03E-07	1.76E-07	-	-
	TGI	7,86E-07	1,19E-06	3,29E-07	4,54E-07	3,23E-07	-	2,14E-05	9,67E-07	3,06E-06	3,07E-06	1,41E-06	4,59E-07	3,92E-07	-	-
	LC50	2,38E-06	3,66E-06	1,13E-06	1,96E-06	5,21E-07	-	4,06E-06	3,24E-06	6,44E-06	5,96E-06	3,32E-06	1,61E-06	1,43E-06	-	-
26	GI50	5.96E-07	9.00E-07	-	6.48E-07	1.99E-07	1.44E-07	7.54E-07	6.84E-07	1.33E-06	2.01E-06	2.03E-07	6.54E-07	1.31E-07	7.01E-07	4.55E-0
	TGI	1,41E-06	1,72E-06	-	1,48E-06	5,14E-07	4,92E-07	1,50E-06	1,48E-06	2,33E-06	5,50E-06	4,55E-07	1,38E-06	2,52E-07	1,57E-06	1,33E-0
	LC50	3,35E-06	3,28E-06	-	3,36E-06	2,04E-06	2,18E-06	2,96E-06	3,19E-06	4,07E-06	5,84E-06	1,89E-06	2,99E-06	4,84E-07	3,51E-06	3,52E-0
27	GI50	6.70E-06	6.70E-06	-	6.70E-06	6.70E-06	3.16E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	3.50E-06	2.14E-06	6.70E-06	6.70E-0
	TGI	6,70E-06	6,70E-06	-	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-0
	LC50	6,70E-06	6,70E-06	-	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-0
28	GI50	2.15E-07	3.63E-07	1.45E-07	3.34E-07	2.28E-07	-	1.47E-06	3.28E-07	1.88E-06	1.48E-06	6.49E-07	1.96E-07	1.72E-07	-	-
	TGI	5,59E-07	1,09E-06	3,36E-07	7,86E-07	3,59E-07	-	2,55E-06	1,04E-06	2,99E-04	2,52E-06	1,54E-06	3,70E-07	3,18E-07	-	-
	LC50	2,09E-06	3,10E-06	1,01E-06	2,55E-06	5,68E-07	-	4,41E-06	4,25E-06	4,75E-06	4,30E-06	3,63E-06	8,72E-07	5,86E-05	-	-

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	H[illegible]A-A
29	GI50	6.70E-06	3.91E-06	-	6.70E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	6.70E-06	5.45E-06	-	6.70E-06	6.70E-0
	TGI	6,70E-06	6,70E-06	-	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	-	6,70E-06	6,70E-0
	LC50	6,70E-06	6,70E-06	-	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	-	6,70E-06	6,70E-0
30	GI50	3.29E-07	8.04E-07	-	2.05E-07	1.92E-07	1.59E-07	1.19E-06	1.04E-06	1.02E-06	2.17E-06	1.73E-07	1.35E-07	1.64E-07	2.12E-07	6.77E-0
	TGI	1,15E-06	1,72E-06	-	3,87E-07	3,50E-07	3,04E-07	2,39E-06	2,24E-06	2,28E-06	5,28E-06	2,99E-07	2,45E-07	3,24E-07	5,42E-07	1,76E-0
	LC50	4,20E-06	3,68E-06	-	1,09E-06	6,37E-07	5,79E-07	4,78E-06	4,81E-06	5,07E-06	6,70E-06	5,17E-07	4,44E-07	6,39E-07	2,47E-06	4,58E-0
31	GI50	3.30E-06	1.94E-06	2.21E-06	2.69E-06	2.69E-06	-	4.21E-06	5.91E-06	2.21E-06	2.12E-06	8.49E-06	8.49E-06	2.38E-06	-	-
	TGI	6,37E-06	3,79E-06	5,03E-06	4,10E-06	4,07E-06	-	8,49E-06	8,49E-06	4,26E-06	3,63E-06	8,49E-06	8,49E-06	4,00E-06	-	-
	LC50	8,49E-06	7,39E-06	8,49E-06	6,25E-06	6,18E-06	-	8,49E-06	8,49E-06	8,18E-06	6,23E-06	8,49E-06	8,49E-06	6,75E-06	-	-
32	GI50	2.12E-06	1.42E-06	2.34E-06	2.29E-06	2.06E-06	-	2.08E-06	5.19E-06	1.91E-06	1.78E-06	7.66E-06	7.83E-06	2.15E-06	-	-
	TGI	3,80E-06	3,08E-06	6,27E-06	3,56E-06	3,26E-06	-	3,63E-06	7,83E-06	4,21E-06	3,12E-06	7,83E-06	7,83E-06	3,66E-06	-	-
	LC50	6,81E-06	6,67E-06	7,83E-06	5,51E-06	5,16E-06	-	6,34E-06	7,83E-06	7,83E-06	5,49E-06	7,83E-06	7,83E-06	6,21E-06	-	-
33	GI50	6.96E-06	-	-	6.96E-06	5.27E-06	-	6.32E-06	9.82E-07	6.96E-06	3.85E-07	4.51E-06	3.99E-06	4.85E-06	9.54E-07	6.96E-0
	TGI	6,96E-06	-	-	6,96E-06	6,96E-06	-	6,96E-06	3,08E-06	6,96E-06	1,70E-06	6,96E-06	6,96E-06	6,96E-06	3,22E-06	6,96E-0
	LC50	6,96E-06	-	-	6,96E-06	6,96E-06	-	6,96E-06	6,96E-06	6,96E-06	5,04E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-0
34	GI50	2.21E-06	-	-	1.41E-06	1.58E-06	-	1.81E-06	1.98E-06	1.34E-06	1.28E-06	1.25E-06	9.04E-07	3.50E-07	1.46E-06	1.59E-0
	TGI	3,26E-06	-	-	2,38E-06	2,56E-06	-	3,01E-06	3,20E-06	2,66E-06	2,58E-06	2,32E-06	1,77E-06	9,73E-07	2,43E-06	2,63E-0
	LC50	4,79E-06	-	-	4,03E-06	4,14E-06	-	5,00E-06	5,17E-06	5,25E-06	5,21E-06	4,30E-06	2,98E-06	2,48E-06	4,06E-06	4,34E-0
35	GI50	9.05E-07	-	-	7.17E-07	6.84E-07	-	1.17E-06	1.24E-07	1.23E-06	7.51E-07	7.71E-07	2.00E-07	1.58E-07	8.78E-07	1.33E-0
	TGI	1,79E-06	-	-	1,53E-06	1,49E-06	-	2,10E-06	9,58E-07	2,30E-06	1,87E-06	1,62E-06	8,04E-07	3,46E-07	1,74E-07	1,31E-0
	LC50	3,53E-06	-	-	3,24E-06	3,26E-06	-	3,79E-06	2,65E-06	4,28E-06	4,67E-06	3,39E-06	2,28E-06	8,71E-07	3,43E-06	6,70E-0
36	GI50	2.66E-07	-	-	1.44E-07	8.52E-07	-	1.54E-07	4.81E-09	4.20E-07	6.62E-09	3.98E-07	1.36E-07	3.00E-07	7.86E-09	8.19E-0
	TGI	6,75E-07	-	-	9,90E-07	1,74E-06	-	7,21E-07	5,14E-08	1,25E-06	2,73E-08	1,21E-06	9,63E-07	9,63E-07	9,50E-08	6,55E-0
	LC50	2,49E-06	-	-	2,50E-06	3,55E-06	-	2,20E-06	9,90E-07	2,90E-06	9,76E-07	2,84E-06	2,44E-06	2,15E-06	7,01E-07	6,55E-0
37	GI50	2.28E-07	-	-	1.65E-07	1.21E-06	-	7.66E-08	1.74E-08	6.84E-07	1.54E-08	3.91E-07	1.14E-07	1.78E-06	1.29E-08	8.88E-0
	TGI	5,81E-07	-	-	8,27E-07	2,24E-06	-	2,76E-07	3,90E-08	1,48E-06	3,12E-08	6,78E-06	1,02E-06	4,30E-06	2,83E-08	2,01E-0
	LC50	1,96E-06	-	-	2,55E-06	4,15E-06	-	1,30E-06	8,13E-07	3,20E-06	6,28E-08	6,78E-06	2,97E-06	6,78E-06	6,20E-08	4,55E-0
38	GI50	1.66E-06	-	-	1.01E-06	1.97E-06	-	8.05E-07	3.07E-07	1.28E-06	2.54E-08	1.16E-06	1.29E-06	1.12E-06	4.60E-08	1.85E-0
	TGI	2,65E-06	-	-	1,89E-06	2,97E-06	-	1,68E-06	9,88E-07	2,28E-06	1,20E-07	2,12E-06	2,40E-06	1,94E-06	1,55E-07	2,88E-0
	LC50	4,22E-06	-	-	3,53E-06	4,49E-06	-	3,55E-06	2,44E-06	4,05E-06	9,88E-07	3,88E-06	4,47E-06	3,36E-06	5,83E-07	4,49E-0
39	GI50	3.48E-06	-	-	1.33E-06	1.29E-06	-	3.39E-06	4.41E-06	1.27E-06	4.10E-06	1.20E-06	8.89E-07	8.89E-07	4.18E-06	2.75E-0
	TGI	6,63E-06	-	-	2,33E-06	2,29E-06	-	6,63E-06	6,63E-06	2,47E-06	6,63E-06	2,16E-06	1,72E-06	1,70E-06	6,63E-06	6,63E-0
	LC50	6,63E-06	-	-	4,11E-06	4,09E-06	-	6,63E-06	6,63E-06	4,82E-06	6,63E-06	3,87E-06	3,34E-06	3,26E-06	6,63E-06	6,63E-0
40	GI50	1.79E-06	-	-	1.04E-06	1.31E-06	-	1.22E-06	3.18E-07	1.23E-06	1.30E-07	9.49E-07	6.64E-07	2.67E-07	6.42E-07	2.28E-0
	TGI	3,06E-06	-	-	1,94E-06	2,24E-06	-	2,27E-06	7,83E-07	2,34E-06	3,01E-07	1,87E-06	1,41E-06	8,23E-07	1,58E-06	5,94E-0
	LC50	5,24E-06	-	-	3,62E-06	3,79E-06	-	4,20E-06	2,45E-06	4,42E-06	8,63E-07	3,69E-06	2,98E-06	2,23E-06	3,86E-06	6,64E-
41	GI50	1.00E-06	2.28E-06	-	7.77E-07	5.15E-07	-	1.23E-06	1.63E-06	5.85E-06	2.69E-06	7.30E-07	1.55E-07	1.26E-07	1.02E-06	1.24E-
	TGI	1,93E-06	6,76E-06	-	1,56E-06	1,35E-06	-	2,20E-06	2,72E-06	6,76E-06	6,76E-06	1,57E-06	7,23E-07	2,53E-07	2,00E-06	2,15E-
	LC50	3,73E-06	6,76E-06	-	3,13E-06	3,16E-06	-	3,96E-06	4,53E-06	6,76E-06	6,76E-06	3,41E-06	2,90E-06	5,09E-07	3,94E-06	3,74E-
42	GI50	6.96E-06	3.03E-06	-	4.61E-06	6.96E-06	6.96E-06	6.96E-06	6.96E-06	1.82E-06	5.08E-06	6.96E-06	3.87E-06	-	6.96E-06	6.96E-
	TGI	6,96E-06	6,96E-06	-	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	4,37E-06	6,96E-06	6,96E-06	6,96E-06	-	6,96E-06	6,96E-
	LC50	6,96E-06	6,96E-06	-	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	6,96E-06	-	6,96E-06	6,96E-

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-A
43	GI50	4.76E-07	8.52E-07	2.41E-07	2.33E-07	1.19E-07	7.80E-07	5.21E-07	1.23E-06	1.79E-06	1.41E-07	1.05E-07	-	3.97E-07	7.93E-0
	TGI	1,34E-06	1,97E-06	7,67E-07	6,28E-07	2,75E-07	1,66E-06	1,40E-06	2,18E-06	4,86E-06	2,73E-07	2,22E-07	-	1,32E-06	1,77E-0
	LC50	3,22E-06	4,55E-06	3,68E-06	2,53E-06	6,34E-07	3,57E-06	3,41E-06	3,85E-06	6,55E-06	5,31E-07	4,71E-07	-	3,95E-06	3,93E-0
44	GI50	3.03E-06	2.78E-06	1.43E-06	1.50E-06	1.19E-06	3.69E-06	2.69E-06	3.06E-06	6.90E-06	1.34E-06	9.73E-07	-	2.85E-06	3.18E-0
	TGI	6,90E-06	6,90E-06	2,86E-06	2,95E-06	2,52E-06	6,90E-06	6,90E-06	6,90E-06	6,90E-06	2,61E-06	2,03E-06	-	6,90E-06	6,90E-0
	LC50	6,90E-06	6,90E-06	5,72E-06	5,77E-06	5,30E-06	6,90E-06	6,90E-06	6,90E-06	6,90E-06	5,08E-06	4,23E-06	-	6,90E-06	6,90E-0
45	GI50	7.31E-07	1.02E-06	3.32E-07	4.21E-07	1.63E-07	1.03E-06	9.25E-07	1.49E-06	2.32E-06	3.16E-07	1.13E-07	-	9.38E-07	9.12E-0
	TGI	1,61E-06	2,35E-06	1,23E-06	1,30E-06	4,10E-07	2,05E-06	1,90E-06	3,10E-06	6,70E-06	1,17E-06	2,32E-07	-	2,16E-06	1,94E-0
	LC50	3,54E-06	5,44E-06	4,02E-06	3,69E-06	1,68E-06	4,11E-06	3,93E-06	6,40E-06	6,70E-06	3,66E-06	4,76E-07	-	4,98E-06	4,13E-0
46	GI50	2.43E-06	2.42E-06	1.50E-06	1.67E-06	1.35E-06	6.77E-06	3.67E-06	3.04E-06	3.12E-06	2.50E-06	1.20E-06	-	4.61E-06	3.30E-0
	TGI	6,77E-06	6,77E-06	3,55E-06	3,62E-06	2,75E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	2,30E-06	-	6,77E-06	6,77E-0
	LC50	6,77E-06	6,77E-06	6,77E-06	6,77E-06	5,62E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	4,40E-06	-	6,77E-06	6,77E-0
47	GI50	6.78E-06	3.45E-06	6.78E-06	6.78E-06	6.78E-06	6.78E-06	6.78E-06	6.78E-06	5.63E-06	6.78E-06	5.85E-06	-	6.78E-06	6.78E-0
	TGI	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	-	6,78E-06	6,78E-0
	LC50	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	6,78E-06	-	6,78E-06	6,78E-0
48	GI50	6.64E-06	3.10E-06	6.64E-06	6.64E-06	6.64E-06	6.64E-06	5.82E-06	6.64E-06	5.10E-06	6.64E-06	5.17E-06	-	6.64E-06	6.64E-0
	TGI	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	-	6,64E-06	6,64E-0
	LC50	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	6,64E-06	-	6,64E-06	6,64E-0
49	GI50	1.09E-06	2.20E-06	1.27E-06	1.91E-06	1.94E-06	1.33E-06	2.61E-06	1.50E-07	1.31E-06	1.58E-06	1.47E-06	3.22E-06	1.10E-06	1.07E-0
	TGI	2,50E-06	6,70E-06	2,75E-06	5,15E-06	5,57E-06	2,50E-06	6,70E-06	1,67E-06	3,09E-06	3,74E-06	3,80E-06	6,70E-06	2,20E-06	2,52E-0
	LC50	5,75E-06	6,70E-06	5,97E-06	6,70E-06	6,70E-06	4,69E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	6,70E-06	4,40E-06	5,95E-0
50	GI50	6.70E-06	6.76E-06	3.76E-06	2.70E-06	8.99E-07	6.76E-06	6.76E-06	6.76E-06	4.16E-06	3.76E-06	1.21E-06	1.27E-06	5.58E-06	6.76E-0
	TGI	6,76E-06	6,76E-06	6,76E-06	6,76E-06	2,58E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	2,80E-06	2,54E-06	6,76E-06	6,76E-0
	LC50	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,47E-06	5,10E-06	6,76E-06	6,76E-0
51	GI50	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-06	6.63E-0
	TGI	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-0
	LC50	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-06	6,63E-0
52	GI50	7.41E-06	-	7.41E-06	3.67E-06	-	7.41E-06	7.41E-06	7.41E-06	6.64E-06	7.41E-06	7.41E-06	7.41E-06	6.18E-06	1.79E-0
	TGI	7,41E-06	-	7,41E-06	7,41E-06	-	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-0
	LC50	7,41E-06	-	7,41E-06	7,41E-06	-	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-06	7,41E-0
53	GI50	7.49E-06	-	7.49E-06	3.31E-06	-	7.49E-06	7.49E-06	7.49E-06	4.17E-06	7.49E-06	5.29E-06	7.49E-06	7.49E-06	7.49E-0
	TGI	7,49E-06	-	7,49E-06	7,49E-06	-	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-0
	LC50	7,49E-06	-	7,49E-06	7,49E-06	-	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-06	7,49E-0
54	GI50	1.49E-06	-	1.11E-06	1.45E-06	-	1.24E-06	1.14E-06	1.31E-06	8.63E-07	1.88E-06	1.08E-06	1.55E-06	8.41E-07	1.08E-0
	TGI	2,62E-06	-	2,09E-06	2,57E-06	-	2,20E-06	2,19E-06	2,40E-06	2,01E-06	3,51E-06	2,14E-06	2,88E-06	1,73E-06	2,04E-0
	LC50	4,61E-06	-	3,92E-06	4,57E-06	-	3,90E-06	4,23E-06	4,41E-06	4,68E-06	6,55E-06	4,21E-06	5,37E-06	3,54E-06	3,88E-0
55	GI50	7.27E-06	-	7.27E-06	7.27E-06	-	7.27E-06	7.27E-06	7.27E-06	7.27E-06	7.27E-06	7.27E-06	7.27E-06	7.27E-06	7.27E-0
	TGI	7,27E-06	-	7,27E-06	7,27E-06	-	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-0
	LC50	7,27E-06	-	7,27E-06	7,27E-06	-	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-06	7,27E-0
56	GI50	1.95E-06	-	2.78E-06	1.39E-06	-	7.11E-06	1.68E-07	7.11E-06	1.18E-07	7.11E-06	2.22E-06	7.11E-06	3.70E-07	7.11E-0
	TGI	7,11E-06	-	7,11E-06	7,11E-06	-	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-0
	LC50	7,11E-06	-	7,11E-06	7,11E-06	-	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-0

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	H[illegible]A-AI
57	GI50	7.18E-06	-	7.18E-06	7.18E-06	-	7.18E-06	7.18E-06	7.18E-06	3.88E-06	7.18E-06	7.18E-06	7.18E-06	7.18E-06	7.18E-0
	TGI	7,18E-06	-	7,18E-06	7,18E-06	-	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-0
	LC50	7,18E-06	-	7,18E-06	7,18E-06	-	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-06	7,18E-0
58	GI50	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-06	7.11E-0
	TGI	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-0
	LC50	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-06	7,11E-0
64	GI50	6.75E-06	1.80E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-06	6.75E-0
	TGI	6,75E-06	3,99E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-0
	LC50	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-06	6,75E-0
65	GI50	1.17E-06	3.48E-06	1.44E-06	8.06E-07	1.16E-06	1.43E-06	1.95E-06	3.00E-06	6.89E-06	1.23E-06	1.03E-06	5.57E-07	1.21E-06	2.23E-0
	TGI	2,28E-06	6,89E-06	2,67E-06	1,69E-06	2,21E-06	3,39E-06	4,99E-06	6,89E-06	6,89E-06	2,54E-06	1,98E-06	1,53E-06	1,99E-06	6,89E-0
	LC50	4,44E-06	6,89E-06	4,96E-06	3,56E-06	4,19E-06	6,89E-06	6,89E-06	6,89E-06	6,89E-06	5,28E-06	3,81E-06	3,81E-06	3,26E-06	6,89E-0
66	GI50	1.36E-06	4.63E-06	1.57E-06	1.21E-06	1.49E-06	2.24E-06	4.96E-06	6.76E-06	6.76E-06	1.28E-06	1.30E-06	1.07E-06	3.17E-06	3.41E-0
	TGI	2,73E-06	6,76E-06	2,82E-06	2,43E-06	2,67E-06	6,14E-06	6,76E-06	6,76E-06	6,76E-06	2,54E-06	2,47E-06	2,26E-06	6,76E-06	6,76E-0
	LC50	5,45E-06	6,76E-06	5,05E-06	4,89E-06	4,77E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	5,06E-06	4,71E-06	4,80E-06	6,76E-06	6,76E-0
67	GI50	9.15E-07	1.83E-06	5.53E-07	3.90E-07	3.20E-07	1.13E-06	1.44E-06	2.92E-06	6.83E-06	3.47E-07	1.73E-07	2.64E-07	1.15E-06	1.09E-0
	TGI	1,77E-06	4,60E-06	1,58E-06	1,33E-06	5,56E-07	2,25E-06	2,70E-06	6,83E-06	6,83E-06	9,63E-07	3,40E-07	5,61E-06	2,15E-06	2,03E-0
	LC50	3,40E-06	6,83E-06	4,59E-06	4,53E-06	2,21E-06	4,51E-06	5,06E-06	6,83E-06	6,83E-06	4,17E-06	6,69E-07	2,47E-06	4,00E-06	3,75E-0
68	GI50	4.70E-07	1.05E-06	8.70E-08	1.50E-07	1.50E-07	1.25E-06	1.56E-06	3.70E-06	6.59E-06	5.12E-07	3.37E-07	2.81E-07	1.03E-06	9.43E-0
	TGI	1,21E-06	2,36E-06	1,98E-07	2,73E-07	3,13E-07	2,17E-06	2,83E-06	6,59E-06	6,59E-06	1,40E-06	9,49E-07	6,47E-07	2,05E-06	1,90E-0
	LC50	2,85E-06	5,29E-06	4,53E-07	4,99E-07	6,55E-07	3,77E-06	5,12E-06	6,59E-06	6,59E-06	3,66E-06	2,62E-06	2,53E-06	4,04E-06	3,82E-0
69	GI50	6.77E-06	2.35E-06	4.37E-06	6.77E-06	6.72E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-06	6.77E-0
	TGI	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-0
	LC50	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-06	6,77E-0
70	GI50	1.42E-07	6.66E-08	1.82E-07	1.12E-07	5.28E-08	1.20E-07	1.83E-07	-	1.00E-06	1.11E-07	6.85E-08	2.85E-08	1.25E-07	2.59E-0
	TGI	2,57E-07	2,08E-07	2,97E-07	2,09E-07	1,18E-08	2,39E-07	3,32E-07	-	1,85E-06	2,13E-07	4,11E-07	8,15E-08	2,22E-07	7,63E-0
	LC50	4,65E-07	6,47E-06	4,87E-07	3,87E-07	2,99E-07	4,75E-07	6,04E-07	-	3,42E-06	4,12E-07	1,73E-06	6,12E-07	3,97E-07	2,24E-0
71	GI50	1.22E-06	3.94E-07	5.26E-07	4.43E-07	2.28E-07	1.52E-06	1.75E-06	-	1.56E-06	3.30E-07	1.66E-07	1.84E-07	8.36E-07	1.33E-0
	TGI	2,11E-06	1,12E-06	1,21E-06	5,35E-07	3,56E-07	2,40E-06	2,62E-06	-	4,41E-06	9,82E-07	2,77E-07	2,90E-07	1,63E-06	2,22E-0
	LC50	3,64E-06	2,70E-06	2,72E-06	8,48E-07	5,54E-07	3,80E-06	3,92E-06	-	6,38E-06	2,67E-07	4,62E-07	4,56E-07	3,16E-06	3,70E-0
72	GI50	1.32E-07	2.70E-07	1.70E-07	2.59E-07	1.25E-07	1.90E-07	2.14E-07	-	8.85E-07	1.20E-07	1.29E-07	4.98E-08	1.33E-07	2.87E-0
	TGI	2,37E-07	8,42E-07	2,74E-07	3,84E-07	2,28E-07	4,05E-07	3,47E-07	-	1,68E-06	2,30E-07	2,35E-07	1,23E-07	2,24E-07	7,73E-0
	LC50	4,25E-07	2,38E-06	4,43E-07	5,70E-07	4,16E-07	1,20E-06	5,59E-07	-	3,20E-06	4,41E-07	4,28E-07	2,74E-07	3,79E-07	2,28E-0
73	GI50	2.33E-07	3.77E-07	1.73E-07	2.29E-07	1.50E-07	2.23E-07	5.32E-07	-	9.52E-07	1.27E-07	1.12E-07	3.35E-08	1.73E-07	5.21E-0
	TGI	6,57E-07	8,41E-07	2,90E-07	3,26E-07	2,94E-07	4,71E-07	1,24E-06	-	1,85E-06	2,32E-07	2,04E-07	9,46E-08	2,80E-07	1,30E-0
	LC50	2,04E-06	2,32E-06	4,88E-07	4,67E-07	5,74E-07	1,48E-06	2,76E-06	-	3,58E-06	4,26E-07	3,72E-07	2,55E-07	4,50E-07	2,95E-0
74	GI50	7.96E-07	4.02E-07	2.06E-07	2.12E-07	2.13E-07	8.29E-07	9.56E-07	-	1.08E-06	1.37E-07	1.39E-07	1.53E-07	2.14E-07	6.75E-0
	TGI	1,61E-06	1,02E-06	3,88E-07	3,18E-07	3,24E-07	1,64E-06	1,76E-06	-	1,98E-06	2,61E-07	2,35E-07	3,09E-07	3,78E-07	1,46E-0
	LC50	3,25E-06	2,59E-06	9,43E-07	4,77E-07	4,95E-07	3,23E-06	3,23E-06	-	3,60E-06	4,99E-07	3,95E-07	6,24E-07	6,86E-06	3,15E-0
75	GI50	7.49E-07	-	3.50E-07	3.80E-07	2.51E-07	9.75E-07	1.03E-06	5.33E-07	1.70E-06	1.58E-07	1.26E-07	1.37E-07	5.09E-07	9.42E-0
	TGI	1,54E-06	-	8,36E-07	9,09E-07	6,03E-07	1,82E-06	1,91E-06	2,15E-06	3,08E-06	2,80E-07	2,22E-07	2,27E-07	1,18E-06	1,78E-0
	LC50	3,16E-06	-	2,36E-06	2,41E-06	2,38E-06	3,40E-06	3,55E-06	6,63E-06	5,59E-06	4,95E-07	3,91E-07	3,79E-07	2,50E-06	[illegible],38E-0

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	SKOV-3	IGROV	IGROV-ET	SK-BR-3	MEL-28	H-MEC-1	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	H[illegible]A-A
76	GI50	1.20E-06	-	-	1.18E-06	1.00E-06	3.13E-07	1.54E-06	-	1.53E-06	1.71E-06	5.93E-06	8.42E-07	2.43E-07	1.47E-07	1.18E-06	1.35E-0
	TGI	2,12E-06	-	-	2,14E-06	1,85E-06	6,26E-07	2,52E-06	-	2,60E-06	4,01E-06	6,74E-06	1,74E-06	7,21E-07	2,61E-07	2,01E-06	2,28E-0
	LC50	3,75E-06	-	-	3,87E-06	3,41E-06	2,04E-06	4,14E-06	-	4,43E-06	6,74E-06	6,74E-06	3,59E-06	2,16E-06	4,63E-07	3,45E-06	3,86E-0
77	GI50	3.63E-06	-	-	1.61E-06	1.42E-06	8.73E-07	1.58E-06	-	1.52E-06	1.70E-06	6.74E-06	1.23E-06	9.13E-07	2.71E-07	1.43E-06	1.57E-0
	TGI	6,71E-06	-	-	2,62E-06	2,34E-06	2,19E-06	3,41E-06	-	2,58E-06	3,99E-06	6,74E-06	2,21E-06	1,76E-06	8,32E-07	2,29E-06	2,53E-0
	LC50	6,74E-06	-	-	4,26E-06	3,86E-06	5,51E-06	6,71E-06	-	4,40E-06	6,71E-06	6,74E-06	3,97E-06	3,40E-06	2,14E-06	3,66E-06	4,07E-0
78	GI50	1.27E-06	-	-	8.77E-07	9.30E-07	2.66E-07	1.12E-06	-	1.27E-06	1.65E-06	2.56E-06	1.08E-06	3.90E-07	1.35E-07	1.16E-06	9.64E-0
	TGI	2,18E-06	-	-	1,71E-06	1,79E-06	1,02E-06	2,01E-06	-	2,23E-06	3,78E-06	6,69E-06	1,99E-06	1,16E-06	2,89E-07	1,97E-06	1,81E-0
	LC50	3,76E-06	-	-	3,33E-06	3,42E-06	2,58E-06	3,59E-06	-	3,92E-06	6,69E-06	6,69E-06	3,70E-06	2,71E-06	6,21E-07	3,36E-06	3,42E-0
79	GI50	6.01E-06	-	-	1.91E-06	1.98E-06	7.96E-07	2.31E-06	-	4.42E-06	1.71E-06	6.75E-06	1.44E-06	5.91E-07	3.87E-07	2.69E-06	4.80E-0
	TGI	6,75E-06	-	-	3,25E-06	4,28E-06	1,65E-06	6,75E-06	-	6,75E-06	4,02E-06	6,75E-06	2,43E-06	1,40E-06	1,15E-06	6,75E-06	6,75E-0
	LC50	6,75E-06	-	-	5,55E-06	6,75E-06	3,43E-06	6,75E-06	-	6,75E-06	6,75E-06	6,75E-06	4,09E-06	3,02E-06	2,56E-06	6,75E-06	6,75E-0
80	GI50	1.07E-06	-	-	4.16E-07	5.83E-07	1.23E-07	1.32E-06	-	1.13E-06	7.44E-07	1.90E-06	1.78E-07	1.25E-07	1.20E-07	3.92E-07	8.45E-0
	TGI	1,97E-06	-	-	1,17E-06	1,39E-06	3,29E-07	2,25E-06	-	2,03E-06	1,62E-06	3,82E-06	4,03E-07	2,61E-07	2,08E-07	1,19E-06	1,64E-0
	LC50	3,62E-06	-	-	2,82E-06	3,04E-06	1,43E-06	3,84E-06	-	3,67E-06	3,54E-06	6,70E-06	1,20E-06	5,45E-07	3,59E-07	2,51E-06	3,19E-0
89	GI50	-	-	-	-	-	-	-	-	3.17E-07	-	-	6.35E-08	-	-	-	-
	TGI	-	-	-	-	-	-	-	-	4,44E-07	-	-	3,17E-07	-	-	-	-
	LC50	-	-	-	-	-	-	-	-	6,35E-07	-	-	5,71E-07	-	-	-	-
90	GI50	-	-	-	-	-	-	-	-	3.05E-07	-	-	6.11E-08	-	-	-	-
	TGI	-	-	-	-	-	-	-	-	4,27E-07	-	-	3,05E-07	-	-	-	-
	LC50	-	-	-	-	-	-	-	-	6,11E-07	-	-	5,49E-07	-	-	-	-
91	GI50	-	-	-	-	-	-	-	-	3.12E-07	-	-	6.24E-08	-	-	-	-
	TGI	-	-	-	-	-	-	-	-	4,37E-07	-	-	3,12E-07	-	-	-	-
	LC50	-	-	-	-	-	-	-	-	6,24E-07	-	-	5,62E-07	-	-	-	-
92	GI50	1.22E-07	4.02E-07	1.57E-07	2.39E-07	2.11E-07	1.58E-07	1.00E-06	9.77E-07	1.33E-07	1.55E-06	3.62E-06	1.48E-07	1.26E-07	1.43E-07	-	-
	TGI	3,32E-07	1,44E-06	4,18E-07	7,68E-07	5,41E-07	3,01E-07	2,00E-06	1,93E-06	2,91E-07	2,84E-06	6,14E-06	3,08E-07	2,44E-07	2,84E-07	-	-
	LC50	1,29E-06	4,19E-06	1,76E-06	2,87E-06	2,84E-06	5,72E-07	3,98E-06	3,83E-06	7,06E-07	5,20E-06	6,14E-06	7,80E-07	4,74E-07	5,66E-07	-	-
93	GI50	6.21E-09	7.95E-07	-	2.14E-07	2.66E-07	-	3.20E-07	-	1.86E-07	1.49E-06	1.11E-06	1.68E-07	8.08E-08	7.82E-08	4.91E-07	6.51E-0
	TGI	1,66E-08	2,16E-06	-	3,90E-08	7,17E-07	-	9,51E-07	-	6,97E-07	2,72E-06	2,08E-06	2,72E-07	2,08E-07	1,82E-07	1,25E-06	1,43E-0
	LC50	4,40E-08	5,88E-06	-	8,66E-07	2,49E-06	-	2,60E-06	-	2,44E-06	4,94E-06	3,90E-06	4,39E-07	5,37E-07	4,26E-07	3,25E-06	3,15E-0
94	GI50	7.18E-07	1.65E-06	-	3.13E-07	2.08E-07	2.26E-07	7.43E-07	-	1.12E-06	1.84E-06	2.86E-06	1.63E-07	1.68E-07	1.62E-07	4.13E-07	6.93E-0
	TGI	1,51E-06	4,92E-06	-	6,11E-07	4,00E-07	3,75E-07	1,50E-06	-	2,28E-06	3,75E-06	6,35E-06	3,43E-07	3,26E-07	3,55E-07	1,16E-06	1,65E-0
	LC50	3,18E-06	6,35E-06	-	3,05E-06	1,58E-06	6,25E-07	3,01E-06	-	4,66E-06	6,35E-06	6,35E-06	1,14E-06	6,32E-07	1,32E-06	3,02E-06	3,92E-0
95	GI50	8.92E-07	1.70E-06	-	1.78E-07	2.19E-07	7.31E-08	1.03E-06	-	1.15E-06	3.57E-06	3.58E-06	8.62E-08	1.25E-07	1.24E-07	1.62E-07	6.17E-0
	TGI	1,73E-06	5,99E-06	-	3,13E-07	3,77E-07	1,95E-07	1,84E-06	-	2,29E-06	5,99E-06	5,99E-06	1,93E-07	2,34E-07	2,41E-07	3,06E-07	1,52E-0
	LC50	3,36E-06	5,99E-06	-	5,50E-07	9,16E-07	5,20E-07	3,28E-06	-	4,55E-06	5,99E-06	5,99E-06	4,32E-07	4,37E-07	4,71E-07	5,79E-07	3,74E-0
96	GI50	9.85E-07	1.73E-06	-	1.84E-07	1.78E-07	6.48E-08	1.22E-06	-	1.26E-06	4.50E-06	6.04E-06	1.01E-07	1.40E-07	1.53E-07	2.44E-07	6.86E-0
	TGI	1,94E-06	4,60E-06	-	3,34E-07	3,32E-07	1,91E-07	2,15E-06	-	2,57E-06	6,35E-06	6,35E-06	2,11E-07	2,64E-07	2,93E-07	7,24E-07	1,62E-0
	LC50	3,81E-06	6,35E-06	-	6,07E-07	6,19E-07	5,60E-07	3,77E-06	-	5,23E-06	6,35E-06	6,35E-06	4,42E-07	5,00E-07	5,59E-07	2,59E-06	3,82E-0
97	GI50	5.17E-07	8.66E-07	-	2.44E-07	2.32E-07	4.55E-08	1.28E-07	-	1.05E-06	1.28E-06	2.64E-06	1.76E-07	1.28E-07	1.86E-07	8.09E-07	7.51E-0
	TGI	1,21E-06	1,81E-06	-	4,64E-07	4,57E-07	1,17E-07	2,21E-07	-	1,96E-06	2,34E-06	5,22E-06	3,36E-07	3,01E-07	3,96E-07	1,78E-06	1,61E-0
	LC50	2,81E-06	3,77E-06	-	2,20E-06	2,38E-06	3,24E-07	3,84E-07	-	3,64E-06	4,27E-06	5,22E-06	1,19E-06	1,09E-06	4,12E-06	3,89E-06	3,44E-0

Table VII (cont.): Activity data (Molar)

		DU-145	LN-caP	IGROV	IGROV-ET	SK-BR-3	MEL-28	A-549	K-562	PANC-1	HT-29	LOVO	LOVO-DOX	HELA	HELA-AI
98	GI50	6.40E-06	3.25E-06	3.90E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	6.40E-06	1.36E-06	1.66E-0
	TGI	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	2,43E-06	3,46E-0
	LC50	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	6,40E-06	4,35E-06	6,40E-0
99	GI50	7.57E-07	1.02E-06	2.68E-07	8.74E-07	1.40E-07	8.39E-07	8.86E-07	3.30E-06	1.50E-06	1.24E-07	1.29E-07	1.39E-07	3.29E-07	9.51E-0
	TGI	1,57E-06	1,99E-06	8,98E-07	1,88E-06	2,84E-07	1,73E-06	2,05E-06	5,87E-06	3,50E-06	2,41E-07	2,53E-07	3,10E-07	1,19E-06	2,10E-0
	LC50	3,26E-06	3,89E-06	2,69E-06	4,04E-06	5,75E-07	3,54E-06	4,76E-06	5,87E-06	5,87E-06	4,67E-07	4,95E-07	3,93E-06	3,51E-06	4,65E-0
63	GI50	1.19E-07	3.36E-07	1.28E-07	7.61E-08	7.48E-08	8.28E-07	7.28E-07	1.48E-06	1.05E-06	1.32E-07	1.22E-07	1.30E-07	1.75E-07	2.92E-0
	TGI	4,25E-07	1,21E-06	4,29E-07	2,01E-07	1,86E-07	1,77E-06	1,60E-06	2,63E-06	2,10E-06	3,22E-07	2,40E-07	2,56E-07	4,99E-07	1,09E-0
	LC50	1,55E-06	2,85E-06	2,00E-06	5,29E-07	4,65E-07	3,79E-06	3,48E-06	4,69E-06	4,21E-06	1,13E-06	4,69E-07	5,02E-07	2,06E-06	3,23E-0
62	GI50	6.43E-06	2.19E-06	6.43E-06	4.13E-06	-	6.43E-06	6.43E-06	6.43E-06	4.55E-06	6.43E-06	3.36E-06	6.43E-06	6.43E-06	6.43E-0
	TGI	6,43E-06	6,43E-06	6,43E-06	6,43E-06	-	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-0
	LC50	6,43E-06	6,43E-06	6,43E-06	6,43E-06	-	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-06	6,43E-0
61	GI50	1.72E-06	9.21E-07	1.36E-06	1.44E-06	-	3.79E-06	2.87E-06	6.49E-06	6.49E-06	1.18E-06	1.20E-06	1.17E-06	3.48E-06	4.93E-0
	TGI	4,24E-06	2,40E-06	2,86E-06	3,30E-06	-	6,49E-06	6,49E-06	6,49E-06	6,49E-06	2,25E-06	2,65E-06	2,71E-06	6,49E-06	6,49E-0
	LC50	6,49E-06	6,26E-06	5,98E-06	6,49E-06	-	6,49E-06	6,49E-06	6,49E-06	6,49E-06	4,26E-06	5,83E-06	6,28E-06	6,49E-06	6,49E-0
60	GI50	1.64E-06	1.23E-06	1.24E-06	1.21E-06	-	1.66E-06	1.61E-06	5.30E-06	6.70E-06	1.04E-06	1.03E-06	6.24E-07	3.15E-06	2.05E-0
	TGI	3,17E-06	2,59E-06	2,79E-06	2,68E-06	-	3,07E-06	3,66E-06	6,70E-06	6,70E-06	2,16E-06	2,44E-06	1,98E-06	6,70E-06	4,42E-0
	LC50	6,16E-06	5,43E-06	6,28E-06	5,95E-06	-	5,68E-06	6,70E-06	6,70E-06	6,70E-06	4,47E-06	5,77E-06	6,14E-06	6,70E-06	6,70E-0
59	GI50	6.76E-06	4.52E-06	6.76E-06	6.76E-06	-	6.76E-06	6.76E-06	6.76E-06	6.76E-06	6.76E-06	5.28E-06	6.76E-06	6.76E-06	6.76E-0
	TGI	6,76E-06	6,76E-06	6,76E-06	6,76E-06	-	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-0
	LC50	6,76E-06	6,76E-06	6,76E-06	6,76E-06	-	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-06	6,76E-0